VOLUME XXIII 1944

MEDICINE

Analytical Reviews

of

General Medicine
Neurology and Pediatrics

THE WILLIAMS & WILKINS COMPANY
BALTIMORE, MD
1944

CONTENTS

NUMBER 1, FEBRUARY, 1944

NUMBER 2, MAY, 1944

NUMBER 3, SEPTEMBER, 1944

NUMBER 4, DECEMBER, 1944

SECONDARY PELLAGRA[1]

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[1] The continuity of this work over the past thirteen years could not have been carried on except for large grants from many philanthropic foundations persons and commercial concerns The major part of the expenses for the past five years have been defrayed by grants from the John and Mary R Markle Foundation, the Martha Leland Sherwin Memorial Fund, and Anheuser Busch, Inc

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I INTRODUCTION

From conception to death man is beset with impediments to optimum nutrition His existence is literally a struggle for food His growth, his development, and his health depend upon the changing fortunes of this contest with nature When the balance is upset unfavorably malnutrition occurs This may be manifest by a complicated array of vague symptoms or by characteristic evidence of a specific deficiency disease It is more than a decade since one of us (T D S) began investigations in the field of nutrition with particular emphasis on pellagra and related deficiency states A by-product of these studies has been the uncovering of many diseases upon which malnutrition becomes ingrafted This has led us to study similar examples in the medical literature on pellagra, consulting more than two thousand articles of which the relevant ones are contained in the bibliography In the light of this experience, it is timely to render an account of our present conceptions of this aspect of the general problem of undernutrition, namely, secondary or conditioned pellagra

Pellagra has been classified as *endemic*, *alcoholic* and *secondary* (28, 336, 338). In the *endemic* class we arbitrarily include patients whose diet is inadequate for any reason, because of poverty, food fads, or ill conceived therapeutic diets *Alcoholic* pellagra is that type which occurs in persons whose calories are derived largely from alcohol with a reduced intake of vitamin-rich foods needed to insure its proper combustion *Secondary* pellagra occurs when some disease interferes with the orderly processes of nutrition in various ways which we will consider To establish an unassailable case for a given instance of secondary pellagra one should be able to demonstrate that· (1) the patient ingested a diet adequate for his ordinary needs, or at least not permitting a recognizable deficiency, (2) some extraneous condition occurred which was followed by the development of pellagra while the same diet was consumed, and (3) when the underlying condition was corrected pellagra disappeared It is manifestly impossible to satisfy these demands when the provoking factor cannot be removed or when the pellagra is relieved with specific restitution therapy, or when, as sometimes happens, it undergoes spontaneous remission We have included in this review many cases of secondary pellagra on evidence which was circumstantial only We believe this is justifiable in the present incomplete state of our knowledge, if only to focus attention upon the multifarious background of bodily disease as an obstacle to proper nutrition

This paper deals with the relationship of well-recognized diseases to the subsequent development of pellagra It has been known for a long time that many abnormal conditions and diseases render the body particularly susceptible to the development of secondary vitamin deficiencies These have been expounded admirably by McCarrison (198) Years ago Manson (216) remarked of beriberi, "given the necessary food restrictions, any lowering of the general resistance of the body may lead to the rapid development of the disease Thus it often makes its appearance during pregnancy, lactation, after surgical operations or during convalescence from infections and debilitating diseases such as dysentery, malaria and enteric " This is equally true for pellagra and other deficiency

diseases Thus the internal, as well as external environment may conspire to bring about a quantitative or qualitative deficiency of essential vitamins It is not sufficient that a person have access to adequate food, but it must be prepared properly and the several necessary constituents must be ingested and absorbed before the body can utilize them Even then certain ideal conditions must prevail for optimum nutrition It is only natural that the powerful instinct of self-preservation in all animals emphasizes the urge to obtain food This trait is so instinctive that one seldom considers the ramifications of its force It is indeed well that such a strong stimulus exists, for in the face of this urge nature may interpose many hindrances within the body as well as outside

Today we are all concerned with the ravages of war and famine, of mass starvation or borderline malnutrition which have existed from time immemorial and continue to exist But before these vast problems can be solved, we must learn what we can of the infinitely complex little world of man's body and the forces holding constant its intricate humoral matrix, for this internal environment must be maintained relatively constant to permit even a little freedom in dealing with the external environment Claude Bernard has emphasized the fact that "all vital mechanisms, however varied they may be, have but one object, that of preserving constant the conditions of life in the internal environment " Processes of normal nutrition constitute the *sine qua non* of a normal homeostatic mechanism Storage of vitamins provides a factor of safety which is the first line of defense against deficiency, but without ample intake of food all stabilizing forces eventually fail Effective barriers between food produced in the outside world and its assimilation into the *milieu intérieur* exist within the body under circumstances of disease With one form of ensuing nutritional disaster this paper deals

II HISTORICAL NOTE

A study of the relationship of specific organic diseases and abnormal states to the subsequent development of a vitamin deficiency syndrome has been possible only since the concept of vitamin deficiency as a cause of disease has been accepted generally For that reason it is not profitable to set down an inclusive review of the fascinating older literature on pellagra, except to point out the complexities of the clinical problems which have given rise to an almost incredible display of imagination regarding etiology To turn the pages of the history of pellagra is to find that ideas about the fundamental disturbances characterizing pellagra have followed the pattern of prevailing medical thought and fancy during the two centuries it has been known When the disease was first described the presence of a poison or toxin in the ingested food was considered a satisfactory explanation for its manifestations Maize was implicated as a poison long before it was considered an incomplete food The concept of poison may have received a stimulus from the well publicized activities of the Borgias and the historic fascination with poisons In the latter third of the nineteenth century the profound revolution in medical thought resulting from the work of Pasteur in establishing the germ theory of infections ' strong con-

viction that pellagra was an infectious disease A tremendous amount of work has been expended in an attempt to isolate a causative bacterium, yeast, fungus, virus or to fix on an intermediate host or vector Certain infectious agents announced as *the* cause of pellagra have proved to be will-of-the-wisps and have now been relegated to the limbo of discredited hypothesis Even the well publicized and widely believed (289) conclusions of Sambon (302, 303) incriminating the buffalo gnat have not passed the test of clinical experiment For sixty years the belief that pellagra was an infectious disease has been a veritable millstone about the neck of progress in understanding the condition

Many observations made in an attempt to establish an infectious cause for pellagra have some justification Pellagra may follow in the wake of infectious diseases Indeed, the very complex and still incompletely understood pathogenesis of pellagra has always been a ready source of confusion Only in recent years has the vitamin deficiency concept of the cause of pellagra been put on a firm basis by combined clinical and experimental studies made possible by the collaboration of many different sciences

We have used our current conceptions of the disease as a background in reviewing the literature concerning secondary pellagra A complete study of all varieties of disease which might be complicated by secondary nutritional disturbances could be encompassed only in a medical encyclopedia All the specialities would pass in review Any disease can predispose to the development of pellagra by deranging the patient's relationship to his external environment The province of secondary pellagra might be considered all-inclusive, taking for its domain all diseases of society as well as those of the human body The disorders of the body politic, giving rise to war and famine, the upheavals in personality leading to food fads, dietary cults, addiction to alcohol and more disabling upsets in sanity are important causes of pellagra and many less severe stages of nutritional failure Conditions such as epilepsy, hemiplegia, Parkinsonism (257, 260) which may be complicated by pellagra, are not considered in this paper All evidence indicates that these as well as alcoholic pellagra have essentially the same pathogenesis as endemic pellagra—a failure to *ingest* ample food Whatever be the mechanism of its production the resulting pellagra is the same disease entity Nor will this study include *endemic* pellagra It will be restricted to pellagra which follows well recognized disease, for the most part organic in nature

III INVESTIGATIONS

The 388 patients with secondary pellagra discussed in this study have been observed in the course of intensive investigations of the various clinical manifestations of vitamin B-complex deficiency disease in human beings These studies were begun in the University Hospitals, Cleveland, Ohio, and subsequently have been in progress in the Cincinnati General Hospital, Cincinnati, Ohio, and the Nutrition Clinic at the Hillman Hospital in Birmingham, Alabama Cases have been included only if characteristic pellagrous glossitis and sym-

metrical dermatitis were present at the time of observation Subclinical deficiency disorders and the syndromes of angular cheilosis and peripheral neuritis are not considered Where studies were incomplete or the diagnosis in doubt, cases were discarded The records include most of the cases of pellagra seen in the two Ohio hospitals for the periods of study ending with 1939 The records from Birmingham include all completely studied cases seen during 1940 and 1941 A special effort was made to investigate all pellagrins in whom it was suspected that some factor other than poor diet was chiefly responsible for their pellagra They constitute only a fraction of all persons with deficiency diseases studied in Birmingham in 1940 and 1941 The classification of cases may be seen in Tables I and II Since the two groups considered are representative of pellagra in the

TABLE I

Distribution of cases

	ENDEMIC	SECONDARY	ALCOHOLIC	TOTAL
Ohio, 1930-39	17	146	115	278
Alabama, 1940-41	272*	242	7	521
Totals	289	388	122	799

* The pellagrins included here were those subjected to special study because it was suspected that some disease might have predisposed to pellagra If the entire group of pellagrins observed at the Hillman Clinic had been considered, the "secondary" column would probably not contain more than one-fourth of the total

TABLE II

Distribution by sex and color

	WHITE FEMALE	WHITE MALE	COLORED FEMALE	COLORED MALE
Ohio	32	37	56	21
Alabama	171	49	18	4
Totals	203	86	74	25

endemic area and in a region where it is generally believed to be uncommon, interesting contrasts stand out A statistical study has not been attempted because the samples are not strictly comparable and could not be related exactly to the populations from which they were drawn Nevertheless, the extreme variations in the pattern of provoking disease suggest significant differences in the two regions where the studies were made

The exact pathogenesis of pellagra is not established It is impossible, therefore, to evaluate the importance of each separate disease or abnormal state in predisposing to or precipitating pellagra Nor is it possible to assign the proportion of blame which should be placed upon deficient diet and some disease process when the combination has existed prior to the development of pellagra

It is probable that some of the diseases we will discuss were not very important factors One of the worst defects in our knowledge of secondary or conditioned deficiency syndromes is want of an explanation of the fact that apparently identical diseases in different persons may be followed by pellagra, or neuritis, or anemia (either iron deficiency or extrinsic factor deficiency), or by no apparent nutritional abnormality This underscores our ignorance of many fundamental aspects of nutrition and metabolism It complicates any attempt to establish minimum dosage of vitamins in therapy and to arrive at some rational estimate of that elusive quantum, the minimal daily requirement Without definite knowledge of the quantity of vitamins needed to protect against a deficiency under varying environmental conditions, it is a far cry to speculate upon optimum amounts Even further afield is a solution to the problem of possible toxicity from dosage far beyond the customary needs of the body These questions are being attacked, however, by the slow and clumsy methods of empiricism

Before we can make a logical study of the basic problem of average daily requirement we must know something of the rôle played by the B-complex vitamins and especially niacin (nicotinic acid) in normal cellular economy Again we have to infer a great deal by analogy All the evidence we have indicates that at least some of the vitamin B factors are essential building stones for respiratory enzyme systems in living cells (98) This has been shown for certain bacteria and yeasts Specific molecules must be delivered preformed in the food since they cannot be built by the cells which need them When they are wanting, oxidation is disturbed because of a failure of essential respiratory catalysts Other functions may exist

When these principles are integrated into an hypothesis concerning vitamin B-complex functions in man we can reduce the problem to one of supply and demand Even without exact knowledge of storage and excretion we can form a picture of the circumstances increasing vitamin requirement If the enzymes built up from these vitamins are mediators of cellular respiration anything which increases tissue oxidation will call for some increase in specific cellular enzymes and their vitamin precursors In pellagra the pyridine coenzymes containing nicotinic acid amide are of primary significance The basic need will be related to age, sex, weight, body surface and total metabolism Growth, gestation, lactation, physical exercise, fever, hyperthyroidism and the burden of parasitic or neoplastic disease will increase the need for these enzymes Inactivity and the absence of the conditions listed above will reduce the requirement Such factors have rarely been considered in approaching the problem of secondary pellagra which has been confined chiefly to diseases of the alimentary canal

This concept permits a logical division of the discussion, depending upon the occurrence of a decreased supply of vitamins from obstruction along the path of intake or increased loss or an elevation of the requirement to satisfy enhanced needs The various headings indicate the utility of such a separation of conditions leading to secondary pellagra In diseases where the reason for a complicating vitamin deficiency is obscure, theoretical considerations are offered

as suggestions Since disease of the alimentary canal is the classical cause of secondary pellagra, this will be considered first

IV DISEASES OF THE ALIMENTARY CANAL

It is not always easy to distinguish between symptoms which result from a vitamin B-complex deficiency and symptoms of an underlying condition which gives rise to it Indeed, in many cases the manifold effects of a secondary deficiency collaborate with an organic disease of the alimentary canal to produce a pernicious cycle of disturbances in gastro-intestinal function which leads to increasingly severe deficiency and perhaps even to death Nausea and vomiting reduce food intake, diarrhea prevents proper digestion and absorption The loss of B complex factors needed for normal alimentary function accelerates the downhill trend (26)

A deficiency of vitamins may arise from functional, as well as organic, disorders of the gastro-intestinal tract A person with an emotional type of alimentary disorder may be as ready a candidate for pellagra as one who has a partially obstructing carcinoma of the pylorus Poorly selected diet, loss of appetite, nausea, vomiting, diarrhea and perhaps constipation, all must be considered as detrimental to adequate nutrition Infections, and metabolic changes in association with neoplastic disease may mediate against proper nutrition by humoral mechanisms which we do not fully understand The simple mechanical factors of obstruction and the inadequate assimilation of food operate in a clear-cut manner The pathogenesis of vitamin deficiencies in abnormal conditions of the alimentary canal has been reviewed frequently in recent years (9, 26, 71, 190, 343, 348, 366) The main ideas in these articles will be recapitulated in brief

Many mechanisms may be involved in the development of vitamin deficiency diseases as a sequel to functional and organic disturbances of the gastro-intestinal tract Since the study of newly synthesized crystalline vitamins in relation to alimentary physiology has been of short duration, many important investigations have not yet been undertaken A tentative outline of mechanisms which may be important in causing pellagra secondary to alimentary tract disease follows

1 *Increased intestinal motility* In a study of vitamin deficiencies in chronic diarrhea consequent upon organic lesions of the gut, we found that ingested dyes or glass beads often appeared in the stool within four hours after they were swallowed (26) This type of gastro-intestinal hypermotility was found in cases where pellagra had developed (209) Rapid intestinal motility may exist in patients with organic lesions before they develop full-blown vitamin deficiency syndromes (26) The food is hurried through the alimentary canal and cannot be digested properly Absorption is necessarily poor We emphasize the loss of foods which contain nicotinic acid, phosphorus and protein, all of which appear to be of importance in preventing pellagra

2 *Decreased enzymatic digestion of food* It has been recognized for a long time that certain diseases of the stomach are associated with a decline in secretion

of hydrochloric acid, rennin, pepsin and other ferments As the food is passed along the alimentary canal digestion begins with material in a more complex state than is the case in normal digestion Certain constituents of the ingested food are not broken down until bacterial action with putrefaction and fermentation occurs in the lower portions of the gut Therefore, absorption of normal end products of digestion is reduced Digestion and assimilation in the lower alimentary canal may be disturbed by any lesion which interferes with normal motility, production of digestion ferments, and the capacity of the intestines to absorb the products of digestion

It has been suggested that a factor proliferated by the stomach and another factor obtained from ingested food interact within the stomach or upper duodenum, to produce a third substance which is essential for the prevention of pellagra Such a process has been advanced by Spies (339), Sydenstricker (350), Stannus (343), and Petri (268, 269, 270) from independent observations In the absence of any demonstration of these still hypothetical factors, it may be assumed that if such an interaction exists it constitutes the synthesis of coenzymes or the conjunction of the codehydrogenases with their protein carriers

3 *Inadequate absorption* Investigations of absorption in chronic disorders of the alimentary canal indicate a reduction from the normal It has been shown that dextrose, galactose, xylose and lactose are poorly absorbed (134, 186, 188) It is probable but not established that there is similar failure of absorption of vitamins Chronically diseased areas in the gut, be the cause infection, ulceration, scarring, atrophy, surgical operation, poor circulation, or fistulae, reduce not only the normal surface available for absorption but interfere with digestion and motility so that the orderly sequences of assimilation are perverted

4 *Abnormal bacterial flora* Many years ago Turner (365) suggested that an important factor in chronic low grade obstruction of the alimentary canal leading to pellagra was the changed bacterial flora in the stagnant region proximal to the obstruction This was especially noted in cases of rectal stricture, but occurred to some extent in obstruction of the colon, cecum or ileum Turner suspected that putrefaction with the liberation of toxic material inhibited or interfered with normal liver function and so poisoned the entire organism The excretion of large amounts of indican in the urine of pellagrins was considered confirmatory evidence of putrefaction of protein within the intestinal canal (319, 320) When pellagra developed as a sequel to alimentary tract disorders it was assumed that the pellagra-preventing element in the food was inadequate for detoxification of hypothetical substances liberated by the disturbed alimentary canal (152) Information obtained since the introduction of nicotinic acid may place these observations in a different light No study has been made of the possible synthesis of nicotinic acid by bacteria in the alimentary canal in man Rats are able to synthesize nicotinic acid and vitamin K from food which contains none or only traces of these substances Various bacteria can synthesize different vitamin B constituents and cattle and sheep are able to enhance the vitamin B content of their ingested ration by bacterial action in the alimentary canal (201)

These observations in animals cannot be transferred to man, but they suggest

the possibility that normal bacterial residents of the alimentary canal, particularly in the colon, may synthesize certain vitamins It is also possible that intestinal bacteria convert vitamins into enzymes or coenzymes which may be absorbed ready made It is likely that variation in bacterial flora explains some of the differences in vitamin requirements among the several species of animals

5 *Destruction of vitamins or utilization by bacteria* Under certain conditions, bacteria in the alimentary canal might *destroy, inactivate* or *use up* vitamins contained in the food Bacillary dysenteries where the infecting agent has a high nicotinic acid requirement conceivably could lead to the development of pellagra by depriving the host of large quantities of nicotinic acid There is no evidence, however, that this occurs in man

6 *Possible inactivation, inhibition or binding of vitamins by dietary constituents* Recent developments in the chemistry of vitamins have revealed a new type of inactivation of vitamins, namely the inactivation of biotin by the egg white protein, avidin, through a very stable chemical combination (91) It is conceivable that certain diets contain proteins or other materials which fix, destroy, or inactivate essential vitamins Some such function for cyanogenic substances has been postulated in "riboflavin deficiency" (63) The notion of "toxins" as positive agents in deficiency disease may come back into importance Future work along these lines holds great promise but in the present connection is altogether speculative

7 *Phosphorylation* The cells of the intestines, just as other cells, have the capacity for phosphorylation It is possible, but it has not been demonstrated, that disturbance of this function in gastro-intestinal disease may favor development of deficiency syndromes Some vitamins of the B-complex are active in enzyme systems only after phosphorylation, but it remains to be demonstrated that pellagra ever follows a primary defect in phosphorus metabolism

8 *Liver damage* The development of pellagra in cases of chronic liver disease has been recognized for a long time This suggests that disorders of the liver may produce vitamin deficiency diseases either with or without an initial disturbance of the gastro-intestinal tract Conversely, the belief that cirrhosis is a deficiency disease is accepted by many workers The liver may transform vitamin precursors into functioning respiratory enzyme systems, and probably forms the carrier protein Its rôle in storage is presumably of importance also

9 *Additional factors* There are important additional factors which increase the risk of secondary deficiency in diseases of the alimentary canal In acute or chronic disturbances of the gastro-intestinal function there may be loss of appetite It may range all the way from mere failure to enjoy food, to the insistent unwillingness to eat anything *Nausea and vomiting* may reduce intake of food, particularly in disorders of the stomach and upper intestine *Infection and fever*, throwing an added burden on the respiratory enzyme systems by increasing metabolism, may be the final insults which precipitate a deficiency disease in clinically recognizable form It is apparent that any antecedent condition which has impaired the nutritional status of the patient will increase the danger of pellagra in the advent of gastro-intestinal disease

A *Mouth and throat*

The development of pellagra as a sequel to deformities of oral structure and disturbances in oral hygiene has been overlooked in texts on diseases of the mouth and on pellagra

1 *Teeth* We have found no comprehensive study of the part played by defective teeth or adentia in leading to dietary deficiency though there is a great mass of literature concerning the effect of diet on the teeth There are, however, many casual references to dental abnormalities preceding the occurrence of pellagra Often changes in diet had become necessary because of impaired biting and chewing When dental repair was not obtained, or consisted of ill-fitting appliances, the victim substituted cereals, mush and soup for a balanced diet containing meats and vegetables

Sandwith (307) in Egypt and Roberts (290) in Georgia emphasized their belief that pellagrins usually have sound teeth and Corkhill (68, 69) stated that the severity of dental caries was in inverse proportion to the severity of pellagra encountered in the Sudan These observations probably hold true for the majority of endemic pellagrins Sutton (349) and Niles (246) have mentioned bad teeth in pellagra, but not as a cause Killingsworth (172), however, believed bad teeth a cause of pellagra and briefly reported a study of this problem Smith and Moore (331) were impressed with caries and pyorrhea as a cause of pellagra, through the agency of focal infection Paul (266) reported a patient who developed pellagra 5 years after removal of the teeth and enforced use of a pultaceous diet Takahashi, Ishkawa, Ogawa and Ida (355) believed the edentulous condition of one of their patients was responsible for the development of pellagra Welfield (383) mentioned a similar case Reed (293), and Parfitt (261) have reported cases where the removal of teeth and tonsillectomy were predisposing factors Mention of dental disturbances interfering with nutrition is found in other papers (68, 326, 366)

Because of the paucity of information regarding the teeth in pellagra, we have undertaken careful studies on this aspect of the problem in the Nutrition Clinic in Birmingham in collaboration with Dr A W Mann (215) We found a remarkably low incidence of dental caries but a rather high frequency of disease of the tissues surrounding the teeth Many patients during the period of developing B-complex deficiencies suffer with nervous symptoms Trivial pains, particularly persistent ones, bulk large in their miserable existence Some persons in such a state may have healthy teeth removed for insignificant pains Others, believing hidden disease in the teeth is the cause of their woe, or upon unfortunate advice, have all the teeth extracted It should not be forgotten that calcium depletion of chronic pregnancy and lactation in many of our patients ultimately caused dental disease and by making it harder to eat served to perpetuate the pernicious cycle of undernutrition

Observations In the Alabama pellagrins adentia was the underlying factor in 6 women and 3 men It was of some importance in dietary restrictions in many others In one twelve year old white girl a chronic abscess of the mandible had reduced the food intake to liquids In the Ohio group extensive caries with

tooth removal and osteomyelitis of the jaw was the prime cause of nutritional failure in four colored women and adentia was the main factor in one white woman There was another whose pellagra followed the restriction of food necessitated by the tortures of an energetically erupting but impacted wisdom tooth One tuberculous white male developed pellagra following a fracture of the jaw and the feeding by tube of a high carbohydrate diet

2 *Diseases of the mouth and throat* Since deficiency of vitamin B-complex constituents may cause various lesions in the mouth, sometimes it is difficult to tell how much is cause and how much result of dietary curtailment Brickman (46) has suggested that Vincent's infection of the mouth is a predisposing cause of pellagra It is certainly a frequent result Shelly (317) believed that thrush predisposed to pellagra Others consider it a symptom In the absence of carefully controlled studies it is proper to reserve judgment concerning such diseases as precursors of pellagra Whatever be their cause they reduce the intake of food and thus enhance depletion

3 *Congenital oral deformities* We have observed pellagra develop in patients with cleft palate, congenital laryngeal stricture and other deformities, but since these patients had mental deficiencies this could not be evaluated as an isolated factor Sandy (308) observed congenital absence of the palate in an insane person who developed pellagra Harelip was mentioned by Clark (64) without comment as to its possible relation to pellagra

4 *Infections* Tonsillitis, streptococcus infection of the pharynx, scarlet fever, diphtheria and other specific infections of the throat usually are not followed by an outbreak of pellagra Ordinarily such diseases are self-limited In cases where nutrition prior to infection has been very poor, infection may be sufficient to lead to the outbreak of a manifest deficiency disease although it is not always possible to place the blame specifically on infection or concomitant reduction of food intake because of painful swallowing or chewing It should be emphasized that morbidity and mortality from specific infections tend to be higher in the poorly nourished than in the adequately nourished Poor nutrition may prepare a favorable ground for infection which in turn makes nutrition still worse Dorsey (89), Guthrie (139), Parfitt (261), Reed (283), Kingery (174) and Sclare (311) have mentioned pellagra complicating tonsillectomy and tonsillitis We have seen 6 cases where pellagra developed after various types of acute infections of the throat with fever and dysphagia (see Table III)

5 *Neoplasms* Davie (80) mentioned carcinoma of the tonsil in a pellagrin but there is no evidence that it preceded the pellagra Many persons suffer nutritional deficiency because of the mechanical disturbances in biting, chewing, and swallowing associated with a carcinoma of the tongue, lips or pharynx Any type of cyst or tumor in the jaw or within the neck, impinging upon the esophagus, or interfering with swallowing, may lead to abnormalities of nutrition

A review of the recent reports on cancer of the tongue revealed no mention of pellagra as a sequel Our only case where a tumor of the mouth led to pellagra was one of adamantinoma of the jaw which mechanically impeded eating Hemorrhage was a contributing factor in this case The belief that cancer of

the tongue is frequently preceded by some vitamin B-complex deficiency gains no support from our clinical studies No instance of buccal or lingual carcinoma has occurred in our patients during the last three years

TABLE III

Alimentary canal

DISEASE OR CONDITION	CASES IN WHICH THE CONDITION WAS THE PRINCIPLE CAUSE			CASES IN WHICH IT WAS AN ACCESSORY CONTRIBUTING FACTOR	WHITE		COLORED		AVERAGE AGE
	Total	Ohio	Alabama		Female	Male	Female	Male	
Tooth extraction, osteomyelitis of jaw, fracture or tumor of jaw	12	3	9	6	4	4	4	—	47
Oral sepsis, abscessed teeth	4	3	1	2	2	—	2	—	30
Repeated tonsillitis and sore throat	6	2	4	1	2	2	1	1	14
Esophagus (obstruction)	2	2	—	2	1	1	—	—	65
Peptic ulcer									
Gastric	6	1	5	3	3	2	1	—	42
Duodenal	2	—	2	2	1	1	—	—	53
Old gastroenterostomy	3	2	1	—	1	2	—	—	49
Gastric carcinoma	4	4	—	2	2	2	—	—	49
Gastric neurosis	5	3	2	3	3	1	1	—	42
Atrophic gastritis	—	—	—	2	—	—	—	—	—
Gallbladder disease	4	4	—	2	2	2	—	—	45
Chronic dysentery									
Bacillary 4 / Amebic 1	5	1	4	3	2	3	—	—	56
Ulcerative colitis	6	4	2	1	2	1	3	—	35
Tuberculous enteritis	—	—	—	2	—	—	—	—	—
Sprue	1	1	—	2	1	—	—	—	47
Celiac disease	2	1	1	—	1	1	—	—	34
"Worms"	2	—	2	3	2	—	—	—	9
Hookworm	2	—	2	—	1	1	—	—	31
Food poisoning	2	—	2	—	2	—	—	—	28
Repeated catharsis	1	1	—	—	—	—	1	—	36
Chronic intestinal obstruction	1	1	—	—	1	—	—	—	35
Rectal incontinence	1	—	1	—	1	—	—	—	60
Rectal stricture	11	2	9	1	1	1	9	—	39
Rectal carcinoma	2	1	1	—	—	1	—	1	41
Fistula-in-ano 5 / Rectal abscess 1 / Recto-vaginal fistula 1 / Fecal fistula 1	8	7	1	1	2	1	5	—	41
Hemorrhoids (proctitis, operation)	6	3	3	4	2	2	1	1	45
Totals	98	46	52	42	39	28	28	3	

B *Esophagus*

1 *Stricture and obstruction* Sporadic cases of pellagra resulting from esophageal stricture have been reported by several investigators The first is that

of O'Leary (252) in 1926 In the same year Sutton (349) mentioned this association In their series, Hein and Merrill (155) found one case, complicated by alcoholism Gastrostomy and dilatation of the esophagus permitted resumption of a normal diet and relieved the pellagra Eusterman and O'Leary (99) have observed similar instances, including cases of esophageal carcinoma, in their extensive studies of pellagra secondary to disorders of the gastro-intestinal tract Recently, Scott (313) has added another Benign esophageal stricture has not been mentioned in any American text on pellagra as a predisposing cause of pellagra, though Harris (152) noted complicating pellagra carcinoma of the esophagus

In two of our cases pressure on the esophagus, once from large lymph nodes of Hodgkin's disease and once from a benign tumor, resulted in obstruction which eventuated in pellagra One additional patient had obstruction from a carcinoma of the esophagus In another, a diverticulum of the esophagus was a complicating factor leading to pellagra

2 *Ingestion of corrosive agents* We have observed cases where the ingestion of acids, alkalis or tissue poisons such as bichloride of mercury, have been followed by the outbreak of pellagra Following ingestion of corrosive material, there is usually a period during which the resulting stomatitis, pharyngitis and esophagitis preclude the ingestion of food and perhaps of fluid for several days If a person is undernourished already, such an event may lead to a clinically recognizable vitamin deficiency syndrome The high carbohydrate content of many liquid foods used in the early stages of recovery increases the need for B complex vitamins without supplying them In the case of bichloride of mercury, often taken with suicidal intent, one should be careful to ascertain the victim's nutritional status prior to ingestion of the poison We emphasize this point because a suicidal attempt may be a manifestation of a pellagrous psychosis rather than the factor which precipitates pellagra In some cases, however, the disturbed alimentation which follows the ingestion of mercury and the associated painful stomatitis and colitis may be the most important factors leading to pellagra

C *Stomach*

One of the first clear-cut examples of secondary pellagra occurred in a victim of carcinoma of the stomach with partial obstruction which interfered with nutrition (293) Although the relationship of cause and effect was not apparent at the time, the report clearly indicates the temporal relationship of the two diseases Disturbances in function and in structure of the stomach have received more attention in studies of secondary pellagra than lesions in any other part of the body They include cardio- and pylorospasm, ulcers, neoplastic diseases of all variety, gastritis either non-specific or resulting from over-use of alcohol, and syphilis of the stomach In fact, almost any disturbance which can affect the stomach has been implicated at one time or another as a cause of secondary pellagra (343) The reasons why abnormal function of the stomach leads to pellagra have been outlined in the first part of this section In certain cases, additional factors play a part Vomiting is apt to be an important accom-

paniment of obstruction in the stomach and the attendant alteration of electrolyte and fluid balances may cause disturbances in other essential functions of the body Remedial or palliative diets may not contain a proper balance of food elements and vitamins so that dieto-therapy actually may increase the danger of a vitamin deficiency (105) Hemorrhage from lesions of the stomach is not a frequent factor in precipitating a deficiency disease, but we have seen an occasional patient with severe or repeated hemorrhage in whom a vitamin deficiency syndrome developed only to clear up after repeated transfusion Such cases usually have other factors which predispose to their deficiency We have not seen uncomplicated hemorrhage result in pellagra

1 *Carcinoma of the stomach* The first clear-cut example was that published by Rolph (293) in 1916 He observed typical pellagra develop during the course of gastric cancer In 1919 Bryan (49) observed pellagra in a patient with a gastric ulcer which had undergone malignant change and produced partial obstruction Following gastrectomy the patient recovered from the pellagra Shattuck (315, 316) mentioned cancer of the stomach in one of 144 pellagrins in Massachusetts, but found that in only one of 500 patients with gastric carcinoma had the diagnosis of pellagra been made

The first comprehension of the relationship was indicated by Bender (30) who reported pellagra in two patients with gastric cancer and stated that this association favored dietary deficiency as the cause of pellagra Sutton (349) and O'Leary (252, 253) mentioned additional cases Klauder and Winkelman (175) found one man with an inoperable carcinoma among their alcohol addicts with pellagra This emphasized the multiplicity of underlying disorders which might be found Turner (365) included two examples of pellagra following gastric carcinoma Takahashi (355) observed a similar case

Great impetus to the study of pellagra in regions where it is not endemic came from the extended observations of Eusterman and O'Leary (99) on *secondary* pellagra In one of their reports they included two cases of cancer of the pyloric end of the stomach, and in other reports mention additional cases Boggs and Padgett (39) mentioned four instances of carcinoma of the gastro-intestinal tract without specifying the location We (26) reported 5 such cases and have seen one additional case Others may be found in scattered articles (33, 85, 145, 146, 326, 329, 343, 348, 351, 363, 366, 367)

Several general remarks are pertinent More than forty cases of pellagra as a sequel of cancer of the stomach have been reported Upon analysis there were twice as many men as women in contradistinction to the proportion in endemic pellagra The average age was significantly higher than in endemic pellagra In many cases, chronic partial obstruction, hemorrhage and operations were factors Most patients did not long survive the appearance of pellagra Thus, the morbidity, complications and mortality of pellagra of this type are more closely related to the underlying disease than to endemic pellagra

2 *Peptic ulcer* Peptic ulcer was not mentioned by the early pellagrologists, even as an incidental finding in pellagra Most instances are in American reports, especially in recent years Ulcer is associated with many functional

disturbances—pain, anorexia, nausea, vomiting The diets chosen for ulcer therapy often have been notoriously ill-conceived as to vitamin content Neusser (244) mentioned old and recent ulcers of the stomach in pellagra and Niles (246) made a similar observation Bryan's patient with cancer of the stomach had suffered from gastric ulcer before the cancer and pellagra appeared (49) Graves (126) observed two patients with peptic ulcer in whom operation precipitated pellagra, while Bender (30) observed a case where operative removal of the ulcer was followed by relief of pellagra Eusterman and O'Leary (99, 100) encountered patients with a large gastric ulcer or multiple gastric ulcers who developed pellagra These authors were the first to record several cases in a single report Meyer's patient suffered from pyloric stenosis complicating ulcer (229) All evidence of pellagra disappeared following radical cure of the stenosis In Dennis' case of cancer, ulcer at the pylorus was the primary lesion (85) Smith and Stevens (329) found 24 of their pellagrins had either ulcer or cancer of the stomach as the initial disorder though their cases were not further separated Others (107, 155, 156, 326, 343, 348, 351, 366) have discussed this association Hawksley (154) was impressed by the poor diet in his patient with peptic ulcer who developed pellagra Two cases of "non-maidic" pellagra in victims of stomach ulcer have been reported recently (368) Musser (242) observed a similar sequel of ulcer and Sippy diet where vomiting was prominent Metheny, Northrop and Brown (228) discovered pellagra in a case with hernia, gastric ulcer and hemorrhage where operation was a precipitating agent Field, *Robinson and Melnick (107) have made a special study of the problem of vitamin* deficiency in peptic ulcer They have observed several cases of pellagra develop during the course of therapy with alkalis and diet

As in carcinoma of the stomach, pellagra secondary to gastric ulcer has been observed more frequently in men than women In our cases, gastric ulcer was the determining factor six times, only once in the Ohio group Only two of the patients were women

3 *Gastritis and related disorders* In no other phase of the problem of secondary pellagra is there greater difficulty in evaluating cause and effect of alimentary disturbances than in cases supposedly due to gastro-intestinal disorders From the very first writings it was recognized that pellagra might produce symptoms referable to any segment of the alimentary canal This has been amply substantiated For this reason one must be careful not to attribute pellagra to "stomach trouble" where this is merely one of its protean masquerades

McCarrison (198) was the first to demonstrate the interconnection of certain food factors with normal physiology of the digestive processes He remarked "in experimental animals on a deficient diet without vitamin B there is loss of appetite, impaired digestion, diarrhea, colitis, unhealthy skin, low temperature, slow respiration, cardiovascular depression, progressive anemia and asthenia long before nervous symptoms are produced Do not these form a disease syndrome, in children especially, which is as familiar as its cause is unrecognized?" Later Burnett and Howe (52) summarized the relation of malabsorption and deficiency diseases, reviewing the literature relating to pellagra Though much

of the evidence they gave for malabsorption may be interpreted as a result rather than cause of pellagra they emphasized the part played by the severe diarrhea in increasing and perpetuating the loss of vitamins

Turner (365) was the first investigator to stress the part played by organic disease of the gastro-intestinal tract in pellagra in the South though there had been several observations on sporadic cases in regions where pellagra was recognized infrequently (30, 170, 250, 251, 253, 293) It was his impression that changes in the flora of the gut proximal to diseased areas led to the absorption of "toxins" Subsequently others (44, 65, 160, 355, 359) have emphasized the role of gastric disorders as potential forerunners of pellagra Thaysen's observations gave a strong stimulus to clinicians in Scandinavia who have contributed many reports of secondary pellagra

After Spies and DeWolf (338) had demonstrated the identity of endemic and alcoholic pellagra it was suggested by Zimmerman, Cohen and Gildea (402) that disturbances of digestion and absorption might exist in alcoholic subjects to such a degree that the anti-pellagra factor might not be absorbed even if eaten in adequate amounts In such instances parenteral administration might be effective This concept implied that the alcoholic beverages damage the digesting and absorbing capacity of the alimentary canal Since pellagra can be relieved in such patients by the use of specific therapy while large amounts of alcohol are ingested this idea has little support but it has not been disproved as an auxiliary factor

Strauss (348) was one of the first to systematize the concept of a primary gastro-intestinal failure, rather than food failure, as a cause of nutritional diseases In his paper entitled "The Role of the Gastro-Intestinal Tract in Conditioning Deficiency Disease The Significance of Digestion and Absorption in Pernicious Anemia, Pellagra and "Alcoholic" and other forms of Polyneuritis," he reviewed the literature of secondary pellagra up to that time He pointed out that although Fenwick (106) had enunciated such an hypothesis in 1880 it remained for Castle (59) to demonstrate the interacting forces involved in the process and to establish by experiment upon human beings a new school of thought in nutrition

Stannus (343, 344), after a careful appraisal of the literature on secondary pellagra, concluded that gastritis was present in some form whenever pellagra followed alimentary tract disorders He was particularly struck by the frequency of hypochlorhydria, achlorhydria and achylia This led him to hypothesize an intrinsic-extrinsic factor interaction operating to prevent pellagra analogous to that preventing pernicious anemia

Neusser (244) and Lombroso (193) long ago pointed out the diminution or absence of free hydrochloric acid from the gastric juice of pellagrins All subsequent observers have confirmed this observation The American reports on this subject have been reviewed by Mulholland and King (238) who contributed a special analysis of the relation of abnormal gastric secretions to other manifestations They concluded that although achlorhydria was very frequent in pellagra, and particularly in the severe variety, it had no obligatory association

with any sign or symptom It was permanent in some and disappeared in others after therapy Lack of free gastric hydrochloric acid may long precede evidence of pellagra or may appear as a manifestation of acute relapse No data are at hand to prove that achlorhydria, even long antedating diagnostic lesions in pellagra, may not be a result of inadequate vitamin ingestion On the other hand many people have achlorhydria for long periods and never develop clinical pellagra or even symptoms suspicious of subclinical deficiency One can simply conclude that achlorhydria, hypochlorhydria and achylia are sometimes predisposing influences, sometimes component parts of the pellagra syndrome A strong chain of evidence should be available to demonstrate that a given case is secondary to achlorhydria Several possible cases have been reported (4, 46, 137, 139, 141, 342, 343)

As an important indication of the harm produced by lack of normal gastric juice, we have found that removal of large quantities of gastric juice facilitates the development or relapse of pellagra when a vitamin B "free" diet is used over long periods (335) Metheny, Northrop and Brown (228) mentioned gastric suction as a possible predisposing factor in one of their pellagrins

4 *Alimentary malabsorption* The problem of alimentary absorption in pellagra is complicated by many poorly understood variables Hereditary predisposition has been implicated by those who believe pellagra develops readily in certain persons with defective powers of absorption Studies of absorption of specific pellagra-curative materials are lacking in normals and pellagrins Indirect evidence there is aplenty Spies and Chinn (340) have shown that pellagra may develop in certain apparently normal persons eating what is for the average person a well balanced diet It is known that absorption of sugars is grossly abnormal in patients with vitamin B complex deficiency diseases and in some this may be restored to normal following proper therapy Whether an inherent absorption defect is a cause of deficiency diseases, as it may be a result, is unknown Many phases of this subject have been discussed by various investigators (10, 26, 36, 40, 73, 134, 141, 182, 188, 196, 210, 214, 227, 276, 288, 313, 348, 350, 351, 365, 366)

Experiments have yielded some information on this problem Lattes (186) has shown that rats on normal diets absorb glucose and xylose at a certain rate whereas, when kept on a diet poor in vitamin B, the absorption falls to a level only 40% of the control value The extensive studies of Petri and his collaborators (268, 269, 270) have shown that in some experimental animals a characteristic "pellagra-like" syndrome develops after gastrectomy This may be prevented or partially relieved by feeding stomach preparations whereas it is not cured by nicotinic acid "Gastroprival" pellagra is similar to dietoprival pellagra in the animals studied This has been used as an argument for belief in an intrinsic extrinsic factor pathogenesis for pellagra That a similar pathogenesis operates in human beings is by no means proved Much of the early work was insufficiently controlled as far as dietary factors were concerned

5 *Syphilis of the stomach* Observers have noted a high incidence of syphilis among pellagrins (13, 14), but the cause and effect relationship has never been

demonstrated There are two reports of syphilis of the stomach, however, complicated by pellagra The first was a case of gumma reported by Turner (365) Eusterman and O'Leary (99) reported the other We have not encountered this combination

D *Duodenum*

The possibility that the duodenum as well as the stomach is important in transforming the vitamins liberated by digestion into more complicated materials has been emphasized by workers who believe that pellagra depends on the failure of interaction between nicotinic acid (an extrinsic factor) and some as yet unidentified factor in the stomach or adjacent duodenum (152) In our experience the only lesions in the duodenum, excepting fistula, which have led to the development of a secondary deficiency disease were those which occurred as a part of some generalized intestinal disease or from an ulcer which had led to pyloric obstruction with its attendant disturbances

Duodenal ulcer was mentioned by Wood (392) and Niles (246) in their texts on pellagra though it was not encountered frequently It was not until the comprehensive studies of Eusterman and O'Leary (99) on pellagra secondary to benign and carcinomatous lesions and dysfunction of the gastro-intestinal tract that duodenal ulcer was considered a potential precursor of pellagra Four of their 13 cases had duodenal ulcer Usually pyloric obstruction, or various operations had further deranged alimentary function Raman observed pellagra following an operation for duodenal ulcer Metheny, Northrop and Brown had a similar case of chronic ulcer where poorly chosen diet predisposed and pellagra followed operation and treatment with parenteral dextrose and gastric suction Other examples are recorded (189, 190, 348, 400)

We have observed pellagra four times as a complication of duodenal ulcer In two patients the onset of pellagra followed a severe hemorrhage The age and sex distribution of reported cases reflected the clinical background of ulcer rather than endemic pellagra

Duodenal feeding has been mentioned (49, 308, 358, 359) In all cases it appears that the underlying lesions rather than duodenal feeding as such were important in the development of pellagra

E *Jejunum and Ileum*

1 *Obstructive lesions* Localized disease of the jejunum is a rarity The only reported case giving rise to pellagra is one of stenosis of the jejunum (365) The ileum, however, has a large surface important in digestion and absorption In addition to typhoid fever several diseases of or in the ileum may be important Nuzum (250) in 1925, was the first to point out that disease localized in the ileum could produce such profound disturbances in nutrition that pellagra resulted He reported two cases of partial intestinal obstruction from annular carcinoma of the terminal part of the ileum complicated by pellagra A similar sequence of events was recorded in a Cabot case report (54) Strauss (348) saw the same result from a scar with partial obstruction Dodd (88) reported

a similar sequel to congenital stenosis of the ileum The underlying lesions in these cases were not recognized until autopsy

2 *Non-specific regional granuloma* Deeks (84) mentioned pellagra as a complication of "chronic ulcerative enteritis" Thrash (362) mentioned two cases of nonspecific inflammatory lesions and atrophy of the gut He believed they were caused by pellagra rather than vice versa Golden (122) reported the first instance of pellagra in regional ileitis, making casual reference to a case in the legend explaining an X-ray film Others (58, 208, 211) have emphasized regional enteritis of the granulomatous type as a forerunner of deficiency syndromes

3 *Tuberculous enteritis* The first demonstration of a possible relation of pellagra to tuberculosis of the intestines was recorded by Bardin (17) who found characteristic lesions after death in 3 of 5 pellagrins Though he emphasized the fact that pellagra also predisposed to tuberculosis the clinical history indicated that the intestinal tuberculosis preceded pellagra in his cases Niles (246) mentioned other cases A special report stressing the secondary nature of the pellagra in tuberculous enterocolitis was published by Ellis (96) He seems to have been the first to state directly the cause and effect relationship Turner (365) emphasized this complication Langworthy's case (183) seems to have been a similar one More recently Brester and Hulst (45) and Musser (242) have reported cases Bean and Spies (26) have shown that in addition to infection the chronic diarrhea in intestinal tuberculosis is an important cause of the pellagra which occurs as a sequel

F *Vermiform appendix*

Pellagra as a sequel to disease of the appendix is rare Where it does occur usually there have been complications such as nausea, vomiting, fever, operation and not rarely abscess or peritonitis Jelks (167) mentioned the frequent occurrence of pellagra following operations for appendicitis Roberts (290) reported appendicitis as a complication of pellagra Harris (150) and Stannus (343) have reported pellagra following operation for supposed appendicitis Not without reserve should pellagra following appendicitis be accepted as secondary because some of the prodromal complaints in pellagra mimic notoriously those of so called chronic appendicitis An operation may be the precipitating incident of a latent pellagra

G *Colon*

1 *Ulcerative colitis* The earliest record of ulcerative colitis followed by pellagra occurs in the article by Deeks (84) with no comment on the association To Barnes (18) goes credit for throwing light on the rôle of ulcerative colitis in producing pellagra He observed it develop in spite of ample diet and believed that the diseased bowel could not absorb adequately the pellagra preventive factors The next report was Turner's (365) Larimore (185) noted a case about the same time, and mentioned two similar cases without details Eusterman and O'Leary (99) observed another Thaysen (357) included a case with

ulcerative colitis The literature contains many scattered references (7, 8, 88, 114, 124, 141, 145, 161, 207, 209, 274, 341, 348) Bean and Spies (26) have shown that exacerbation of the diarrhea in ulcerative colitis may result in development of lesions of pellagra which clear up with control of the diarrhea while the diet, exercise and other factors remain constant Several cases of ulcerative colitis leading to pellagra are mentioned in Harris' text (152) He goes so far as to say that "any patient with ulcerative colitis should be regarded as a potential pellagrin " The syndrome of *mucous colitis* as a cause of pellagra has been mentioned (108, 135, 152, 348, 349) It appears the mechanism is the same as in ulcerative colitis One should remember that spastic colon and mucous stools may be a sequel of pellagra and vitamin deficiency, part of the clinical picture rather than a cause

2 *Gastrocolic shunts* In addition to the not infrequent occurrence of pellagra after gastroenterostomies acquired surgically, cases have been reported complicating other shunts Mackie, Eddy and Mills (211), Bean and Spies (26), and Eusterman (101) have seen this sequel to gastrocolic fistula and gastro-jejunocolic fistula In these cases the rôle of hypermotile diarrhea seems to be prepotent A recent report by Gray and Sharpe (127) includes 9 cases of pellagra following in the wake of malfunctioning gastro-jejunocolic fistulae They present evidence that the serious nature of this deformity and its surgical treatment may be largely the result of complicating vitamin deficiency

3 *Carcinoma* Pellagra has been reported as a sequel of disease processes in various portions of the colon Carcinoma with obstruction, hemorrhage, anemia, metastases and occasional operation, is frequently implicated The first reported case was Elliott's (94) 'The lesion was in the cecum The patient was relieved of the pellagrous manifestation by dieto-therapy before succumbing to the cancer Other cases are on record (26, 77, 99, 141, 152)

Turner (365) has seen pellagra occur in a patient with *stenosis of the cecum* Thaysen (357) observed pellagra in a woman with *megalocolon* We have seen pellagra develop in a child with Hirschprung's disease (24)

4 *Hypermotile diarrhea* The role of hypermotile diarrhea in nutritional failure has been reviewed (26, 211) This problem is difficult because diarrhea is a manifestation as well as a cause of pellagra For this reason it has been impossible to evaluate much of the older literature Though Deeks (84) and Lambert (180) observed instances of diarrhea followed by other signs of pellagra, Burnett and Howe (52) appear to have been the first to suggest that diarrhea might be a cause of pellagra in man Boggs and Padgett (39) observed 3 cases of pellagra developing in the course of a chronic diarrhea Turkish prisoners in Egypt in World War I got pellagra only if they had disease of the gut with diarrhea Similar reports have come from India Other instances are given (44, 141, 178, 264, 326, 328) The majority of cases of pellagra developing as a result of chronic diarrhea are discussed under the disease causing the diarrhea

5 *Bacillary dysentery* Though dysenteries caused by various bacilli are not diseases confined to the colon, the most intense disturbances occur in the colon Pellagra is not recognized as a frequent sequel of bacillary dysentery unless it becomes chronic

Sambon (303) was the first to point out that pellagra might follow in the wake of dysentery though he did not report any cases Deeks (84), Manson-Bahr (218) and Roberts (291) also observed pellagra during the course of dysentery Yang and Hu (395) and later Yang and Huang (396) reported from China pellagra occurring as a sequel of chronic bacillary dysentery Biggam and Ghalioungui (35) stressed various enteric diseases forming the substratum of pellagra in Egypt and mentioned bacillary dysentery Panja (259) observed the same sequence of events in India Greenfield and Holmes (130) were the first to record the type of infecting organism (B Shiga) in their case of pellagra Pasha (264) extended the findings of Egyptian observers with a report of 9 cases of "dysentery" In American literature the only report of several cases of pellagra following dysentery was by Bean and Spies (26), who observed three instances Of these two were Flexner and one Shiga Dodd (88) observed a case in a colored child ten months old

H *Rectum*

1 *Rectal stricture* The association of pellagra and rectal stricture is frequent Almost invariably the lesion develops as a consequence of lymphopathia venereum and nearly all reported victims have been colored females Including our 11 instances, 51 cases are recorded In the Southern States where both conditions have been prevalent for years the part played by rectal stricture as a cause of pellagra was not emphasized It remained for Joyce and Seabrook (171) to report the first case In their patient hemorrhoidectomy 7 years previously had resulted in a rectal stricture After increasing nutritional disability pellagra finally appeared Next Crutchfield (77) reported 4 cases In a study of lymphogranuloma, Von Haam and Lichtenstein (140) reported pellagra in 7 colored female patients with rectal stricture Fourteen per cent of the colored patients with stricture (all females) had pellagra at the time they were observed Since pellagra has not been reported as a result of lymphogranuloma in males it is certain that the rectal stricture and its attendant lower bowel disturbances are responsible, rather than any systemic effect of the disease such as the changes in plasma globulin Other cases have been seen (26, 114, 225, 274, 313, 351) Harris (152) is inclined to attribute pellagra in these cases to liver disease arising from a hypothetical toxin liberated from the colon In the absence of specific evidence to the contrary it may be assumed that rectal stricture results in disease of the bowel with some obstruction and a deficiency of nicotinic acid and other factors follows from disordered digestion and absorption

We have observed pellagra in 9 colored women with the rectal stricture of lymphopathia venereum One elderly white woman with rectal stricture complicating the removal of the uterus and radiotherapy for carcinoma developed pellagra The other patient was a white male in whom stricture followed an untreated fistula Of the 51 recorded cases all but 3 were colored females The average age was 29 years A representative case follows

Case report E W , 28 year old colored female seen in Birmingham, Alabama in 1940 Her grandmother died of pellagra, but there was no other history of deficiency disease For the last five years the patient had been troubled by chronic diarrhea associated with a rectal

stricture resulting from lymphopathia venereum Her first attack of pellagra occurred two years after this began Her diet had been moderately deficient in proteins, calories, calcium, phosphorus and iron as well as the B-complex vitamins She had been troubled with insomnia for more than a year and had visual and auditory hallucinations for several months Vaginitis was a source of distress and there had been only two normal menstrual periods within the last two years She had occasional episodes of dizziness, blurred vision and lacrimation When first seen in March, 1940, she had pellagrous dermatitis and glossitis, photophobia, pain and edema of the lower extremities She was extremely weak and had lost much weight, weighing only 86 pounds at the time of the examination The tongue was fiery red and painful and there were whitish areas with piled-up sodden debris where Vincent's organisms were found in great numbers There was redness of the posterior pharynx similar to that of the tongue The lips, especially the lower one, revealed cheilosis, and characteristic angular stomatitis appeared at the corners of the mouth The skin of the hands and feet showed advanced pellagrous dermatitis Neurological examination revealed such indications of neuritis as spontaneous pain and pain on pressure over the calves, very weak knee jerks and absent ankle jerks Biopsy of the terminal portion of the internal branch of the anterior tibial nerve was taken on May 22, 1940 It revealed extensive loss of myelin She was treated with pyrazine monocarboxylic acid, 1 gram a day for 3 days, and the same amount of nicotinic acid amide for the next 4 days There was improvement in the tongue and in the general condition, though not complete relief. Pains in the legs persisted Fifty milligrams of thiamine were given intravenously every day for 10 days and the leg pains ceased Subsequently administrations of riboflavin, pantothenic acid and pyridoxin were followed by further improvement in the general condition, but she did not recover completely and continued to have very severe diarrhea The serum proteins were below normal, but did not increase in spite of a high protein, high vitamin diet Although given large quantities of yeast, the patient did not recover completely It was impossible to bring her to a condition where an operation might have helped

This case reveals the difficulty in treating multiple deficiency diseases when there are lesions in the gastro-intestinal canal which disturb its function Injections of vitamins are valuable in such cases but it is manifestly impossible at the present time to supply all the nutritional requirements by parenteral means only

2. *Carcinoma of the rectum* Shattuck (315) reported an instance of pellagra secondary to carcinoma of the rectum in 1923. Another case was observed by Sydenstricker (351) and we have observed 2 cases

3 *Fistula-in-ano* Turner (365) observed a case of pellagra in a patient with fistula-in-ano We have observed five cases In three, rectal abscesses occurred, and chronic infection complicated the picture In one there was also a rectal stricture

4 *Recto-vaginal-fistula* Lambert (180), Turner (365) and Scott (313) have each observed instances of rectovaginal fistulae which eventuated in pellagra We have seen one case

5 *Cloaca* Turner (365) has observed a case following this rare deformity

6 *Fecal fistula* Sutton (349), Walsh and Norton (381) and Davies and McGregor (81) have observed pellagra in patients with long-standing fecal fistula We have observed pellagra once when this condition followed operation on the uterus

7 *Rectal abscess* Turner (365) observed pellagra in this condition We have observed two instances of pellagra complicating anal fistula and rectal abscess

8 *Hemorrhoids* Hemorrhoids are not mentioned in the literature in association with pellagra We have observed 6 instances where this seemed to be the most important predisposing cause Particularly was this true when there had been severe hemorrhage and one or more operations interfering with sphincter control

9 *Rectocele and cystocele* We have observed a single instance of a multipara who developed pellagra following prolonged and severe incontinence from a combined rectocele and cystocele with local infection

10 *Rectal polyp* A case of rectal polyp which caused diarrhea and eventuated in pellagra was observed by Scott (313) Immediately following removal of the polyp the diarrhea was relieved and the pellagra disappeared

11 *Intemperate or repeated catharsis* As long ago as 1847 Calderini (55) observed pellagra develop as a sequel to repeated self-inflicted purgation A similar association was recorded in the writings of Strambio (347) The significance of this observation was not understood and it was soon forgotten Stannus (343) recently has mentioned over-use of laxatives and cathartics We have made use of this procedure in attempting to induce clinical signs of vitamin deficiencies With a subject eating a diet poor in B vitamins, repeated catharsis induced by castor oil or epsom salts reduces the time required for the development of pellagra This is most readily demonstrated in causing relapse of pellagrins in remission (24)

I *Pellagra secondary to parasitic disease of the intestines*

Discovery of many parasites in the stools of pellagrins contributed one of the many puzzling problems when pellagra was considered to be an infection Some believed various parasites to be the specific causative organisms while others believed they were only secondary invaders in a debilitated host The first reference to parasites in pellagra was made by Strambio (347), who mentioned finding lumbrici in the esophagus and stomach of a pellagrin Other references appear in early European reports (150) Reports on pellagra in Egypt had emphasized the important predisposing influence of various intestinal parasites It should be pointed out that the only evidence of the secondary nature of the pellagra is the clinical observation of time relationship In some instances it is not unlikely that the parasites discovered were themselves secondary invaders similar to monilia infestation so often found in sprue We will consider here the parasitic diseases most often complicated by pellagra

Amebic dysentery

Separation of amebic from bacillary dysentery and distinction between pathogenic and non-pathogenic amebae were established early in the 20th Century The association of dysentery with pellagra was observed soon after the recognition of pellagra by American physicians Allen (5) was first to report amebae in the stools of pellagrins He was seconded by Siler and Nichols (319, 320) who found amebae in five times as many pellagrins as controls under the same conditions

Long (194) reported that 50 of 52 pellagrins examined by him had amebae in the stools Thorington (361) emphasized this association Young (398) went so far as to state that "amebae are found in every case of pellagra at some stage of the disease" Wood (392), Roberts (290) and Lynch (197) each noticed the bad effect of amebiasis on pellagra and vice versa Ormsby (255, 256) voiced the opinion that amebae were a coincidental finding The extensive studies of the Thompson-McFadden Commission (322, 323, 324) emphasized the rôle of chronic dysentery in paving the way for pellagra Jelks (168, 169) has maintained stoutly that amebic infestation is the specific cause of pellagra

During the past decade there have been many reports Viswalingam (378) emphasized this condition in India Yang and Hu (395) and Yu (399) observed amebae in pellagra in China Fakhry (163) found that 63 of 65 pellagrins had amebae, twice the incidence in control groups One or more cases where amebic infestation antedated pellagra have been recorded frequently (6, 22, 26, 46, 50, 67, 83, 93, 113, 264, 294, 295, 300, 313, 318, 342, 365, 398)

Hookworm

The distribution of hookworm and endemic pellagra are very much the same the world over, suggesting a relationship between them It is of interest to recall that pellagra was first identified in Egypt by Sandwith (305, 306, 307) in patients with hookworm disease Similarly in the Southern States, H F Harris (148) reported a case of ankylostomiasis in a patient presenting typical signs of pellagra Simonini (325) in Italy found that 80% of all children with pellagra were infested with hookworm Sambon and Siler later identified this as the European variety of hookworm Sambon (303) said, "ankylostomiasis is undoubtedly of importance as a predisposing factor" in pellagra This has been emphasized repeatedly Knight (176) reported that of ten pellagrins in one family, 8 had hookworm Siler, Garrison and MacNeal (323) were impressed with its importance in children Parrish (263) advocated thymol as a cure for pellagra because of its efficacy in pellagrins with hookworm infestations The world-wide importance is reflected in the reports from many countries (6, 7, 35, 43, 92, 114, 203, 222, 237, 246, 264, 286, 290, 317, 361, 364, 378, 387, 393, 399)

In association with Dexter, we (87) made a careful study of intestinal parasites in pellagrins in Alabama In 110 cases examined, hookworm ova were recovered in only one instance, which indicates that in this particular locality hookworm does not *now* appear to be an important contributing cause of pellagra

Schistosomiasis

The association of pellagra with schistosomiasis was first recorded by Sandwith (304, 307) in his classical studies of pellagra in Egypt His tables indicated that pellagra was more serious in schistosomiasis than in uncinariasis The reasons for this complication of trematode disease are not difficult to understand First it occurs among the poverty ridden fellaheen who are exposed to conditions in which parasitic infestations and malnutrition are rife The disease itself may interfere with nutrition by causing rectal stricture or fistula Secondary

infection and hemorrhage contribute to what often becomes a profound anemia Finally the associated cirrhosis may become severe and further impair the nutrition of the host

Biggam and Ghalioungui (35) have reported their extensive studies in Cairo and found that 94% of all of their pellagrins had some parasitic infestation, with bilharziasis leading the list Other reports (8, 267, 317) confirm these findings Fakhry (103) found the incidence of *Schistosoma mansoni* in pellagrins twice that of the general population Pasha (264) also has found schistosomiasis the most serious parasitic disease from the risk of secondary deficiency syndromes

Other parasitic diseases

Many other parasites have been found in the excreta of pellagrins (206) A good summary of the early work appears in Robert's text (290) Ascaris, Trichuris, Strongylus (158), Hymenolepis, Pin worm, Cercomonas, Trichina, Cestodes, and various flagellates have been reported Doubt may be expressed as to whether pellagra was invariably the complicating factor in these conditions or whether the parasite found a debilitated host It is clear that there may have been a pernicious cycle in some cases Any intestinal parasite may abstract nutrition from the host, aggravate diarrhea or contribute in other ways to a secondary pellagra

Among the other reports of intestinal parasites predisposing to pellagra should be mentioned those of Jelks (168, 169) Findley (109) has reported a case secondary to giardiasis and Wyjasnowsky (399) one with lamblia and trichomonas intestinalis Cases in ascaris infestations have occurred (7, 162, 269, 399) McIntosh (202) recorded pellagra in a two-year-old child infested with hymenolepis nana He suggested that the parasites might cause a secondary vitamin deficiency by acting as "vitamin robbers," holding priority on the ingested food Machwiladse (206) has emphasized various parasitic diseases as a prominent cause of pellagra in Russia Round worms (392) and oxyuriasis (271) have been mentioned as causes of pellagra

J *"Functional" disorders of the upper alimentary canal*

Nutritional disorders have a twofold relation to dysphagia, and spasm of the esophagus or stomach Such disorders, arising from emotional or psychic causes, may result in severe nutritional failure On the other hand, B-complex vitamin deficiencies may be marked by symptoms of difficult swallowing, vomiting or regurgitation which are relieved by proper vitamin treatment The Plummer Vinson syndrome has been considered both a cause and effect of vitamin deficiency (166)

There can be no doubt that globus hystericus and other conditions associated with pharyngeal or esophageal spasm may be sufficiently severe to interfere with adequate nutrition Cases where dysphagia antedated any diagnostic evidence of pellagra are recorded (141, 153, 246, 366)

Marsh (223) has reported pellagra due to cardiospasm We have seen cardiospasm, pylorospasm, hysteria and the so called gastric neurosis followed by

profound derangements of normal alimentary physiology that pellagra resulted The fact that relief of the neurosis and restoration of normal alimentary function was followed by remission of the pellagra indicates it was secondary pellagra In other cases, however, these symptoms disappeared following vitamin therapy and correction of dietary faults

1 *Long-standing gastro-enterostomy* In the early days of surgical enthusiasm short-circuiting operations were devised for amelioration of disease involving various portions of the alimentary canal Complications often followed the most extreme procedures Some of the patients with acquired alimentary deformities have become test subjects for study of the pathological physiology of digestion and absorption.

Roberts (290) reported the first case of pellagra following a gastroenterostomy There was intestinal obstruction and morphine addiction to complete the picture In an article entitled "Pellagra Secondary to Lesion of the Stomach interfering with Nutrition," Bender (30) observed pellagra following gastro-jejunostomy A similar observation was made by Sutton (349) who reported a patient with stomach ulcer who had undergone two gastro-enterostomies and subsequently developed pellagra O'Leary (254, 255) emphasized the malfunctioning stoma after such operations as part of the mechanism leading to pellagra

Guthrie (139) observed among his alcoholic pellagrins one with an old gastroenterostomy which had been followed by severe digestive disturbances Hein and Merrill (155) found pellagra in a patient with an old history of peptic ulcer on whom two gastro-enterostomies has been done 13 and 10 years previously. Eusterman's (100) patient had an old operation complicated by a gastro-jejunal ulcer with hemorrhage A second operation was followed by pellagra which was relieved by diet Later Eusterman and O'Leary (94) reported four patients with pellagra following the disordered nutrition resulting from gastroenterostomy In two cases a duodenal ulcer had been present but in the others no reason for the operation was known Morawitz and Mancke (235) reported another instance Levy Simpson (189, 190) reported a case where a two-thirds gastrectomy and gastroenterostomy for duodenal ulcer had been followed by pellagra This patient had been a vegetarian for 14 years Ellison (97) though emphasizing a curious complication in his case of pellagra, noted that there had been an enterostomy some years previously Norgaard (247, 248, 249) has written extensively of pellagra following gastroenterostomy Yudkin, Hawksley and Drummond (400) observed a case which developed 5 years after a gastroenterostomy for a duodenal ulcer Maasen (205) reported another, the first reported case of this type of pellagra successfully treated with nicotinic acid There are others (121, 152, 228, 292, 301, 312, 313)

We have observed three examples of pellagra as a sequel of surgical short-circuiting operations These cases have several features in common The patient suffered from peptic ulcer of long duration which had not responded to medical management Operation was followed by no improvement and the symptoms of pain, nausea, vomiting and loss of appetite increased The diet

was then curtailed further Gradually upon these symptoms the syndrome of incipient pellagra developed with still more emphasis upon disordered alimentary function Finally the diagnostic skin lesions appeared These patients usually had high levels of gastric HCl In several instances marginal ulcers developed In some, hemorrhage and further operations added a deleterious influence One cannot place the blame for nutritional breakdown on any single factor Loss of surface for secreting digestive juices and for absorption, abnormalities of motility, alterations in normal bacteria, probably all have importance

2 *Gastrectomy and gastrostomy* The possible mechanisms involved in Levy Simpson's case of partial gastrectomy with secondary anemia and pellagra were thoroughly discussed in his review (190) Robertson and Cleveland (292) have reported pellagra appearing about two years following gastrectomy Another case has been reported by Hein and Merrill (155) and Incedayi (165) The following case is included because pellagra developed after removal of most of the stomach This seemed the most important contributing cause, though there were additional complicating factors

D H (U 93567), a 45-year-old colored laborer was admitted to the medical service of the Cincinnati General Hospital on April 27, 1938 For the previous year he had vague symptoms of indigestion with a sensation of uneasiness in the epigastrium after eating but no well localized pain, for the last three months nausea and finally vomiting He had lost 40 pounds within the year A mass was felt in the epigastrium Roentgen studies demonstrated a pyloric *obstruction He was transferred to the surgical service, explored, and a* subtotal gastric resection done Histological study confirmed the clinical diagnosis of carcinoma of the stomach The postoperative course was complicated with nausea, vomiting and periods of hiccough though the operative wound healed and there was no evidence of internal hemorrhage Within a week of the operation he began to run a spiking fever Clinical evidence of pulmonary tuberculosis appeared Within two weeks of operation he complained of having a sore tongue When examined 19 days after operation it was found that he had pellagrous glossitis, stomatitis, and dermatitis of the hands and perineum The abdomen was distended There was some restlessness, lack of attention and at times complete disorientation with delirium In addition he had developed a Virchow's node and X rays of the lungs revealed a patchy diffuse infiltrate which continued to spread Later cavitation occurred An attempt was made to give yeast but this induced gagging and retching Nicotinic acid was then administered in doses of 100 mg 6 times daily There was a rapid response of the tongue and mucous membranes of the mouth, some clearing of the mind and relief from the abdominal distention In spite of this he gradually failed His cough raised sputum with many tubercle bacilli Fever and dyspnea increased There was some jaundice at the time of death 15 weeks after the operation No autopsy was done

From a review of this man's story it is apparent that his nutrition was seriously impaired some months before his stomach was resected Loss of appetite, vomiting, diarrhea, fever, cough and expectoration of much sputum were complications Nevertheless, administration of nicotinic acid in large oral doses was followed by restoration of the oral mucosa to normal This is of interest because Petri (268, 269, 270) has shown that gastropriva l pellagra in animals is not relieved by nicotinic acid but responds to stomach preparations Our single case proves that pellagra in an almost completely gastrectomized man

may be relieved by nicotinic acid but the complicating presence of pulmonary tuberculosis and possible liver necrosis or carcinoma may have supplied the body with other essential constituents leeched from autolyzed cells.

Obstruction

Complete obstruction of the alimentary canal, if uncorrected, is not compatible with life Only with chronic partial obstruction is nutrition apt to be disturbed long enough for a deficiency syndrome to develop In the literature on pellagra many such cases are reported O'Leary (252) made the first study of pellagra due to *obstructive lesions* in the gastro-intestinal tract He said, "the obstructive lesion plays essentially a mechanical rôle, in that it prevents the ingestion or retention of sufficient food or food containing enough vitamins The influence of these obstructive lesions in producing symptoms of pellagra is evidenced by the rapid disappearance of the signs of the disease following surgical removal or relief of the obstruction As a rule the patients are so ill that operative interference is attended with a high mortality " He mentioned malfunctioning gastroenteric stoma, gastric ulcer, stricture of the esophagus, and carcinoma of the esophagus, stomach and bowel as forms of obstruction which might be complicated by pellagra Strauss (348) has seen pellagra complicate diaphragmatic hernia.

Crutchfield (77) found that 10% of his cases of secondary pellagra had gastric obstruction Fisher (111) observed one similar case Boggs and Padget (39) found carcinoma of the gastro-intestinal tract in 4 of their 31 cases of secondary pellagra Meyer (229) and Mulholland and King (238) saw pellagra in pyloric stenosis Wyjasnowsky (394) recorded 4 cases of sporadic pellagra in obstructing carcinoma of the alimentary canal Strauss (348) and Sydenstricker (351, 354) encountered pellagra in upper and lower intestinal obstruction Bean and Spies (26) mentioned one case where adhesions developing after repeated operations led to partial intestinal obstruction and pellagra resulted This case is now reported in detail

A F (U 4426), a 35-year-old unmarried white woman was admitted to the surgical service of the Cincinnati General Hospital on January 26, 1938, for repair of a broken down abdominal wound, and intermittent intestinal obstruction Twenty years before admission she had an operation for a ruptured appendix with a very stormy course following operation Two years later gradually increasing intestinal obstruction led to a second operation This was only partially successful and three years afterwards another operation was undertaken to correct the trouble caused by extensive adhesions and scars For the next 9 years there were episodes of low-grade obstruction From time to time the wounds on the abdomen would break down and small amounts of dark material would be discharged With careful attention by her family physician the wounds healed, only to open later Several minor operations were done on recurring sinuses and the abdomen was opened twice During the few weeks before entry there had been increasing obstruction, and shortly before admission there was a brisk hemorrhage from the most persistently recurring sinus Owing to the severe abdominal pains, obstruction and distention, there had been some restriction of food intake with a notable reduction of meat for several weeks

Physical examination revealed a woman of the stated age who did not look very sick The temperature was 99° F , pulse 68 and respirations 22 to the minute and arterial blood

pressure 115/80 The abdomen was covered with scars distorting the contour in a bizarre pattern In the right rectus area one of the scars gaped open but there was no eviseration, and only a scant inflammatory reaction Roentgen studies revealed the presence of two foreign bodies near the anterior abdominal wall The urine was normal and blood studies gave no indication of anemia or leucocytosis

Course After two weeks of preliminary care a search was made for the foreign bodies under general anesthesia One was found and removed along with scarred skin and granulation tissue The postoperative course was smooth Two weeks later a hemorrhoidectomy was done with no complication She was almost ready for discharge when signs of obstruction recurred A Wangensteen tube was used for several days without improvement Finally it became necessary to do another laparotomy Many adhesions were liberated and the obstruction was relieved There was postoperative ileus, vomiting and some fever Large quantities of dextrose were given by infusion Three days later, severe glossitis and mild pellagrous dermatitis of the hands appeared They were relieved very rapidly by nicotinic acid therapy and it became possible for her to consume an ample diet The fever, ileus and signs of pellagra all disappeared and the abdominal wound subsequently healed and she was discharged in excellent condition

Comment As in many other cases of secondary pellagra it is not possible to assess each element of the combination of disturbances which eventuated in pellagra Obviously organic disease of the bowel and abdomen was the main contributing factor As a result there was voluntary restriction of eating and a further curtailment from loss of appetite, nausea and vomiting Each operation seemed to make the general condition worse The final emergence of pellagra was undoubtedly facilitated by the operation, anesthesia, vomiting, ileus, fever, gastric suction and parenteral dextrose

K *Sprue and idiopathic steatorrhea*

Until we understand the pathogenesis of sprue, it is difficult to establish a cause and effect relationship between sprue and pellagra It is apparent, however, that lesions diagnostic of pellagra may occur in the course of sprue or idiopathic steatorrhea A specific deficiency, if responsible for the sprue syndrome, might eventuate in changes interfering with the utilization of water-soluble vitamins as well as faulty digestion or absorption of fat-soluble ones Thus pellagra might be secondary to sprue At any rate, the similarities in sprue, pellagra and pernicious anemia have been apparent ever since these diseases have been recognized Wood (292) suggested a common etiologic factor in pellagra and sprue This has been seconded by Castle and Rhoads (285), and Harris (150) Bennett, Hunter and Vaughan (31) reported two instances of pellagra complicating idiopathic steatorrhea Bing and Broager (36) have reported improvement of diarrhea in sprue with nicotinic acid therapy, suggesting a secondary deficiency Ungley (366) mentioned the terminal nutritional disasters in nontropical sprue Lightwood and Smallpiece (192) reported an instance of pellagra developing as a sequel to celiac disease There are other reports (227) We have reported 2 cases complicating sprue in which the glossitis and dermatitis of pellagra were relieved by nicotinic acid while the diarrhea of sprue continued Mackie, Eddy and Mills (211) mentioned other cases

As a working hypothesis one can assume that a specific deficiency, probably of

a vitamin B complex factor, is responsible for sprue When this deficiency has lasted long enough, functional or organic changes occur in the alimentary canal hindering utilization of many substances, primarily the fat soluble ones, but also water-soluble materials such as sugars and B-complex factors When a failure to assimilate them obtains long enough, signs of pellagra appear In our clinic there is inadequate evidence for Manson-Bahr's suggestion that sprue is a manifestation of inefficient function of the jejunoileal segment of the gut (217, 219) The assumption that "ileocolic inefficiency" is the specific underlying "lesion" in pellagra is not supported by the present study

Food poisoning. We have seen pellagra develop in a victim of "food poisoning" with severe vomiting and diarrhea He was the most violently ill of several persons in an outbreak and the only one to develop pellagra Similar cases are reported (35)

V HEPATIC DISEASE

Hepatic disease bears a twofold relation to vitamin deficiency disease—it may be result or cause Though the latter postulate is not so certain in man, an increasing body of fact has established it for several experimental animals on variously deficient diets The perplexing question of the cause of cirrhosis may be solved by further work along the present lines of dietary study A comprehensive review of the problem of vitamins, alcohol and cirrhosis by Jolliffe and Jellinek (170a) concludes that none of the deficiency hypotheses of etiology of cirrhosis is sufficiently well documented to be accepted as proved The common denominator of current ideas embodies the concept of some deficiency as the main cause of cirrhosis Perhaps the best evidence in regard to B-complex deficiency and hepatic dysfunction is that of Rhoads and Miller (284) and Patek But until the clinical evidence is better in the case of human cirrhosis we must reserve judgment

The other relation of chronic hepatic disease to vitamin deficiencies is better substantiated This is the case where cirrhosis or other disorders of the liver have secondary vitamin deficiency syndromes engrafted upon them Pellagra is a relatively common sequel of cirrhosis Later researchers may show that cirrhosis is a deficiency disease, but it is equally clear that it may produce nutritional disorders of a secondary nature Since cirrhosis is relatively uncommon as a terminal event in the life of an endemic pellagrin it is improbable that cirrhosis, if a deficiency disease, is caused by the same deficiencies which cause pellagra Whatever the cause, the effect may interfere with several processes essential to health Among these may be listed those associated with perverted metabolism of vitamin K and prothrombin, the anemias, the abnormal manufacture of body proteins, secondary endocrinopathies and a breakdown in sundry mechanisms of detoxifying

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3 *Abscess* An instance of pellagra developing in a patient with liver abscess was mentioned by Wood (392) who quotes the report of the Illinois Pellagra Commission We have seen one case Corlette (70) reported pellagra engrafted upon suppurating hydatid of the liver

4 *Acute yellow atrophy* We have seen one instance of pellagra appearing in a victim of cirrhosis and superimposed hepatitis

5 *Hepatoma* In one of our patients cirrhosis complicated by hepatoma had eventuated in pellagra There is one other report of such a case (220)

VI SURGICAL OPERATIONS AND ANESTHESIA

The occurrence of pellagra following surgical operations was observed very early in the period of intensive study of the disease in America Surgeons also casually noted that operations might make established pellagra worse Saunders (309) in 1909 advised against any but the most urgent operations in pellagrins because of the notoriously high mortality Roberts (290) said in 1912, "a surgical operation or a confinement may float a latent pellagra" At the same symposium Babes (13) reported two patients in whom diagnostic lesions of pellagra appeared after a herniaplasty and lithotomy Wood (392) referred to a woman in good circumstances who developed pellagra after a gynecologic operation On the other hand he had seen apparent relief of pellagra following a similar procedure The first paper especially devoted to this problem was that of Guerry (136) He believed that the operation and anesthesia shared the blame In an article entitled, "Pellagra as a Post-Operative Manifestation," Valk (369) reported an initial outbreak of pellagra appearing in a 52-year-old white woman on the third day after removal of a diseased uterus Nausea and vomiting did not occur, but diarrhea set in and became progressively worse He mentioned two similar cases A reiteration of this same sequence was made by Jelks (167) who stressed operations for appendicitis H F Harris (150) made casual reference to the development of pellagra following an operation for supposed appendicitis There was no recurrence following a subsequent operation on the gall bladder, but the attending circumstances are not known Goldberger (120) emphasized operations precipitating pellagra and urged surgeons to eschew unnecessary surgical procedures where latent pellagra was suspected Graves (126) mentioned the postoperative outbreak of pellagra in three patients suspected of having peptic ulcers In two the diagnosis was verified All three developed manifest signs of pellagra within 48 hours of the operation No other details are available In recent years interest has centered on the underlying lesions in the stomach or intestines, or the changes attendant upon surgical correction of such faults rather than an operation *per se* as the precipitating agent Tissue trauma, infection and perhaps a specific or nonspecific inhibition of respiratory enzymes by anesthetics may all be conducive to a flare-up of latent pellagra Complications such as nausea, vomiting, anorexia, starvation, fever, use of large quantities of dextrose for caloric requirements and forcing fluids to the point of diuresis all may upset nutrition (204) The underlying disorder in alimentary canal disease often has produced chemical vitamin deficiency prior to operation

An apparently uncomplicated operation and convalescence, however, may precipitate pellagra (77) Hudson (169) stressed the very serious nature of any surgical procedures in an untreated pellagrin and reiterated the extremely bad prognosis The report by Bender (30) of pellagra occurring in a patient with a benign gastric ulcer, during the period of jejunal feeding is interesting because after operation and a return to a balanced diet the pellagra was relieved O'Leary (252) and Eusterman (100) and later Eusterman and O'Leary (99) gave an excellent account of secondary pellagra which occurred when operation was undertaken for gastrointestinal disease The sequence of events indicated that surgical procedures had accelerated or precipitated the development of pellagra

TABLE IV

External agents (surgical, traumatic, miscellaneous)

DISEASE OR CONDITION		CASES IN WHICH THE CONDITION WAS THE PRINCIPAL CAUSE			CASES IN WHICH IT WAS AN ACCESSORY CONTRIBUTING FACTOR	WHITE		COLORED		AVERAGE AGE
		Total	Ohio	Alabama		Female	Male	Female	Male	
Surgical operations										
Hysterectomy	6									
Pelvic disease	4									
Colostomy	2									
Hemorrhoids	2									
Pulmonary lobectomy	1	20	5	15	10	17	2	1	—	30
Gall bladder	1									
Tonsils	1									
Appendix	1									
Hernia	1									
Prostate	1									
X ray and radium therapy		5	2	3	1	4	1	—	—	47
Accident		3	2	1	—	1	1	1	—	56
Burn		1	—	1	—	—	1	—	—	5
Forst bite		1	1	—	—	—	1	—	—	13
Totals		30	10	20	11	22	6	2		

in recognizable form It is noteworthy that there was a very high mortality in all patients with secondary pellagra This naturally was influenced by the prognosis of the primary disease

Many reports make incidental mention of pellagra following in the wake of surgical procedures Ellis (96) stressed the role of diet and nausea, vomiting and anorexia, in patients with operations who develop pellagra These cases are more pertinently discussed under the heading of the underlying cause Strauss (248) and Stannus (213) mentioned several examples of pellagra after operations on the viscera The latter author thought ether anesthesia might have some particular influence Golden (122) casually referred to a patient with resection of part of the ileum for regional ileitis in whom pellagra appeared

post-operatively Hanssen (144) discussed a case which followed resection of the stomach for carcinoma Metheny, Northrop and Brown (228) reported a case where an operation for peptic ulcer was followed by pellagra Bean and Spies (26) mentioned colostomy and its attendant alterations in alimentary physiology as a precipitating cause There are other instances of operation on the gut followed by pellagra (75, 155, 279, 313, 341, 381, 349)

Pellagra developed shortly after operation 20 times and in 10 other cases operation was an important complicating agent in our material It was twice as frequent in the Alabama as in the Ohio group This reemphasizes the danger of surgical procedures in incipient or subclinical pellagra The data are summarized in Table IV One sees the preponderance of females and the scarcity of negroes In 12 instances the operations were done for disorders peculiar to females, hysterectomy 6 times, pelvic disease and its sequelae 4 times, and dilatation and curettage twice The other operations were represented once each except for hemorrhoidectomy *Gynecological conditions were frequent* Saunders was the first to emphasize the peculiar liability of pellagrous or prepellagrous women to suffer from symptoms referred to the pelvis In most of our patients pelvic lesions were found at operation but some had complaints without apparent organic cause The operative procedures, including those only contributory to the major precipitating factor are listed below

Gyneological operations	Hysterectomy	6
	Pelvic gonorrhea	4
	Dilatation and curettage	2
	Tubal pregnancy	1
Alimentary canal	Hemorrhoidectomy	4
	Gastroenterostomy	2
	Colostomy	2
	Gastrectomy	1
	Rectal carcinoma	1
	Anal fistula	1
	Tonsillectomy	1
	Appendectomy	1
	Hernia repair	1
	Gall bladder removal	1
Miscellaneous	Pulmonary lobectomy	1
	Prostatectomy	1
	Thyroidectomy	1

The following is a representative case report

G M (U 88140 C G H), a 25-year-old single white girl was admitted to the surgical service of the Cincinnati General Hospital on February 9, 1938, for a lobectomy to relieve chronic bronchiectasis of the left lower lobe

History Beginning at the age of 3 she had had a chronic cough productive of sputum which was foul upon occasions The sputum gradually increased in volume She felt well nonetheless and was able to go to school, but could not engage in strenuous games She had no fever, no hemoptysis, and no sweats at night Six months before admission she had

an appendectomy under gas ether anesthesia Convalescence was complicated by severe coughing which induced vomiting and pain in the abdomen She lost 10 pounds during this period The increase in coughing may have resulted from an exaggeration of her cough always induced by lying flat Two months before entry she had lipiodol and X-ray studies which indicated congenital bronchiectasis of the left lower lobe Her diet had been adequate, except for the period after her appendix was removed when nausea and vomiting associated with paroxysms of cough effectively reduced her intake of food At the time of admission she had regained the 10 pounds lost after appendectomy

Examination revealed physical signs compatible with bronchiectasis and atelectasis of the left lower lobe There was no evidence of recent weight loss and no suggestion of a vitamin deficiency The temperature was 99 8° F (rectal), pulse rate 88, respirations 20 per minute and the arterial blood pressure was 110/65 mm of Hg The leucocyte count was 15,000, red cell count 4 5 million per cubic millimeter and the hemoglobin 11 5 grams On the fifth hospital day a lobectomy was performed under cyclopropane anesthesia She stood the operation well A transfusion of 500 cc of citrated blood was given after the operation The course for the next 10 days was stormy Infection developed in the chest and it was necessary to institute tidal drainage Vomiting occurred after almost every attempt to eat so that very little of the high caloric, high vitamin diet was retained She was given several large injections of dextrose A Wangensteen tube was kept in place for several days after operation The temperature rose to 102° F on several occasions Cough was productive of much foul smelling sputum There was constipation and distention Morphine and codeine were used to control the pain When seen ten days after operation there was typical pellagrous glossitis and mild pharyngitis Vincent's organisms were found in a smear made from a small ulcer in the buccal mucosa There was a mild erythema of the dorsum of the hands and elbows though the patient had been exposed to the sun rarely since the previous summer Her urine showed abnormal pigments by the B E S method (29)

A most dramatic response followed the intravenous administration of 25 mg of nicotinic acid daily for one week The temperature gradually fell to normal, the cough, sputum and drainage from the empyema cavity diminished The tongue became normal, and Vincent's organisms could not longer be demonstrated after the second day Her appetite became ravenous and she retained the food with no difficulty Bowel activity became regular and spontaneous Abnormal pigments disappeared from the urine She ultimately made a complete recovery

Discussion This example of secondary pellagra illustrates many of the nutritional hazards of the post-operative period First, there was a long-standing infection which had undoubtedly reduced the margin of safety in vitamin stores It is likely that a chemical depletion with subclinical deficiency existed though no suggestive sign was detected prior to operation As a large factor in the deficiency must be reckoned her nearly complete starvation for several days after lobectomy Anorexia, nausea, vomiting, constipation and gaseous distention were very troublesome This blockade to the intake of food was of great importance in the ensuing deficiency The effect of the suction tube is harder to evaluate It is probable that the gastric phase of digestion was interfered with Achlorhydria may be a factor in predisposing to the development of pellagra We have found that in human beings whose diets are restricted to foods with little or no natural B complex vitamins removal of large quantities of gastric juice accelerates the development of recognizable signs of vitamin deficiency (21) Administration of dextrose parenterally or carbohydrate orally may bring out a latent deficiency (24) With these factors present it is not

possible to judge the ill-effects of the operation or anesthesia *per se* in provoking the pellagra Whether the tidal drainage or the loss of material in the sputum actually enhanced the nicotinic acid depletion remains speculative This case emphasizes the many ways in which nutrition may be disturbed by surgical disease and treatment It again emphasizes the multiplicity of complications which interfere with nutrition and the difficulty in assigning blame to any isolated factor It also indicates the inadequacy of present day methods of appraising the nutritional status in people without obvious deficiency disease

VII INFECTIONS

One of the historic sources of confusion in interpreting the nature of pellagra resulted from its occurrence as a complication of infections Outbreaks in the wake of epidemics were not easily explained by those who denied that pellagra was an infection Infections have been known to result in exacerbations or even first outbreaks of pellagra since the days of Casal (57) In fact, so close was the association that one school of pellagrologists firmly advocated infection as *the* cause and the ensuing prolonged and vexed search for the specific miasm, contagion, parasite and intermediate host, bacterium or virus has tested the skill, patience and credulity of a host of workers (23, 148, 149, 150, 296) While it was realized in the distant past that any severe, acute or chronic infection interposed an obstacle to proper nutrition, it is only in recent times that the pathogenesis of vitamin deficiency states in such circumstances has been based upon logical premises If one accepts the argument that many vitamin deficiency states are characterized by a disorder of respiratory enzyme functions it follows that an increased load on metabolism will accentuate any disparity between supply of and demand for respiratory enzymes This thesis has been elaborated by Cowgill (71) for vitamin B_1 Infections put a strain upon the cellular catalysts at the very time when other obstacles to proper nutrition occur Anorexia, nausea and vomiting, failure of proper digestion, constipation and distention shift the balance unfavorably Separate types of infection and disease states exert their own peculiar influence in disturbing the normal processes of nutrition

Whether *fever* as distinct from infection ever produces pellagra has not been demonstrated No association between artificial hyperthermia and pellagra has been reported nor have we seen any case We have seen one instance where glossitis followed a course of malaria inoculata for paresis (24) Pellagra has followed vaccine therapy and the ensuing artificial fever (261) but other factors were involved in these cases

There is scant information concerning other means whereby fevers upset the internal mechanisms concerned with utilization of food Some years ago it was demonstrated by Bergland and Chang (32) that infection and fever might cause achlorhydria, the duration and severity of which bore some relation to that of the fever. This would erect an additional barrier to proper nutrition Smithburn and Zerfas (334) have reported a parallel observation of the inhibiting effect of infection and fever on the response of pernicious anemia to adequate

liver therapy A characteristic response followed the abatement of the complicating illness Rhoads (285) has mentioned this phenomenon

It is conceivable that infections exert a specific harmful function on tissue respiration in the sense that bacterial organisms compete with body cells for essential nutrients—or proliferate toxins which inhibit particular steps in the oxidative process These are enticing speculations Until conclusive evidence is at hand, non-specific factors impeding nutrition, and those accelerating general metabolism and tissue respiration suffice as an explanation for the disastrous nutritional sequels to infections and fevers In the words of H F Harris (150), "any and every agency that tends to lower vitality and causes deterioration in the general health plays an important role in the production of pellagra "

1 *Pneumonia* Until the modern period, pneumonia, particularly bronchopneumonia, was commonly found in autopsies of persons who died of pellagra This was emphasized by Lombroso (193) and other Europeans Though Babes (13) mentioned a possible case, it has been only in recent years that pellagra developing as a sequel to pneumonia has been noticed O'Leary (234) mentioned it in 1927 Pollock and Barborka (273) recorded a similar instance Spies (336) stressed this clinical relationship Additional isolated case reports or comment on this sequel to pneumonia occur (285, 332, 351) A possible explanation for this result was offered by Vilter, Bean, Ruegsegger and Spies who found that in some cases of pneumococcal pneumonia the coenzyme I and II content of the blood was low Following crisis there was a rise to normal levels Unfortunately no similar studies were made on any patients who happened to develop pellagra after pneumonia, so this point needs further study before conclusions are drawn It is certain that fever and anorexia as well as the constipation and distention in pneumonia disturb nutrition and contribute to the impoverishment of the stores of vitamins and, in those with poor nutrition, make the risk of pellagra or other deficiency syndromes real

We have observed pellagra follow pneumonia in 18 instances A high proportion was seen in the Ohio group Colored males were strongly represented Pneumonia was the chief infection leading to pellagra (see Table V) In one case pellagra occurred as the sequel of post-pneumonic empyema

2 *Malaria* Many early pellagrologists noted an association between "swamp fevers" and pellagra Some even advocated the use of quinine for pellagra because of the improvement in pellagrins with malaria which followed the use of quinine So it was that long before the cause of either was known it was realized that malaria could be complicated by pellagra Lombroso (193) first stressed the rôle of malaria in predisposing to pellagra, noting that the incidence of pellagra was unusually high in malarious districts In 1882 Strachan (346) observed an outbreak of peripheral neuritis, pellagra and what we now recognize as other deficiency diseases in a group of Jamaican natives Most of his patients also had malaria Though the diagnosis in his cases has been a choice subject for dispute it seems most probable that these ill nourished natives developed multiple vitamin deficiencies in the wake of a devastating outbreak of malaria Sambon gave impetus to the concept of *secondary* pellagra by emphasizing the various

predisposing diseases He quoted the observation of Severi on the "unprecedented increase in the prevalence and severity of pellagra" immediately following the epidemic of malaria which developed in an Italian district when a tributary of the Tiber overflowed and produced a swamp When the swamp was drained the malaria and pellagra disappeared *pari passu* A similar episode had been observed in the Po Valley by Devoto (86) in 1901 Agostini (1) reported the same thing in Umbria Wood reported one of the early cases of pellagra in the United

TABLE V

Infections

DISEASE OR CONDITION	CASES IN WHICH THE CONDITION WAS THE PRINCIPAL CAUSE			CASES IN WHICH IT WAS AN ACCESSORY CONTRIBUTING FACTOR	WHITE		COLORED		AVERAGE AGE
	Total	Ohio	Alabama		Female	Male	Female	Male	
Lobar pneumona	18	12	6	3	8	3	2	5	44
Malaria	13	—	13	2	6	6	1	—	36
Influenza	7	1	6	4	4	1	1	1	36
Pulmonary tuberculosis	6	6	—	8	—	—	4	2	31
Septic abortion	4	1	3	2	3	—	1	—	30
Bronchiectasis 3 / Lung abscess 1	4	2	2	3	—	1	1	2	45
Furunculosis	3	1	2	1	—	3	—	—	56
Chronic sinusitis	2	—	2	4	1	1	—	—	50
Septicemia				5					
Fever unknown origin	1	—	1	4	—	1	—	—	35
Abscess	1	—	1	4	1	—	—	—	6
Undulant fever	1	—	1	—	1	—	—	—	23
Meningitis	1	—	1	—	1	—	—	—	9
Gonorrheal arthritis	1	1	—	—	—	—	1	—	27
Chronic osteomyelitis	1	—	1	5	—	—	1	—	64
Pyelonephritis	1	1	—	3	—	1	—	—	50
Liver abscess	1	1	—	—	—	—	1	—	36
Childhood diseases: Whooping cough	4	—	4	3	1	3	—	—	8
Childhood diseases: Mumps	3	—	3	2	1	2	—	—	18
Childhood diseases: Measles	2	1	1	—	1	—	1	—	8
Totals	74	27	47	53	28	22	14	10	

States under the title "A Mixed Infection with Tertian and Quartan Malaria occurring in a patient with Symmetrical Gangrene" In his text (392) he emphasized the part of malaria in preparing the way for pellagra Similar reports have come from many malarial districts (13, 14, 84, 221, 351, 361, 364, 378, 387) There is a considerable overlapping of the endemic regions of malaria and pellagra (82) Both diseases are apt to occur among people whose economic plight is grim Poverty and ignorance combine to enhance their misery Where conditions can be improved by public health measures such as mosquito control and dietary improvement the morbidity and mortality from malaria and pellagra are conspicuously reduced

Malaria was the chief contributing cause of pellagra in 13 of our cases, all in Alabama In most instances the malaria had been treated inadequately or not at all

3 *Pulmonary tuberculosis* In pulmonary tuberculosis we have an opportunity to study the relationship of chronic infection to malnutrition and pellagra An association was recognized of old (104, 179, 193, 347) This information came from autopsy material and did not stress any cause and effect relationship Case reports give no relevant details from which it is possible to decide A special study by Dell Rosa (222) did not provide crucial evidence on this point

Early studies by American investigators referred to this association (72, 110, 230, 280, 382, 386, 401) Babes (13) listed this complication in a number of case reports The first strong emphasis of a possible direct connection came from Green (128) who reported 25 cases of tuberculosis among 131 of pellagra Bardin (17) observed a patient whose pellagra and tuberculosis improved simultaneously during sanitarium treatment Siler, Garrison and MacNeal (323) noted tuberculosis among the general depressing agents favoring the outbreak of pellagra Sandy (308) mentioned it H F Harris (150) did not believe, however, that pulmonary tuberculosis was a frequent forerunner of pellagra in the southern United States Geck (115) brought forward strong evidence that tuberculosis might be an important cause of pellagra, and noted an especial susceptibility among women He saw pellagra follow the pulmonary, peritoneal and intestinal type of disease Many other reports occur (39, 51, 113, 137, 151, 156, 251, 351, 357, 396, 399) It is probable that fever and anorexia together explain most of the cases Stannus (343) cites Faber to fortify his belief that tuberculosis predisposes to pellagra by causing gastritis

Six colored patients in the Ohio group had pellagra secondary to pulmonary tuberculosis There was none in the Alabama group This is in sharp contrast to malaria

Other forms of tuberculosis In addition to intestinal tuberculosis several instances of pellagra complicating tuberculous peritonitis have been reported (61, 113, 279, 349) Foerster (112) has observed it in miliary and joint tuberculosis

4 *Typhoid fever* Among the many controversies which have left their scars upon the history of pellagra, one of the bitterest was that concerning the nature of "Typhoid pellagra" It is idle to try to reconstruct from vague records and indefinite descriptions the true nature of many of the reported cases Probably some so diagnosed were simply that profound and terrible cachexia which seals the doom of any severely ill pellagrin not adequately treated Other cases seem to be examples of the ravages wrought upon typhoid patients by inanition under the dictum, "Starve a fever" Indeed, from descriptions it seems possible that the so called typhoid tongue was sometimes the early glossitis of incipient pellagra (388) At any rate, cases reported as typhoid pellagra may have been severe typhoid complicated by pellagra, or pellagra complicated by typhoid fever or just terminal pellagra It was not until 1880 when Venturi (374) pointed out the occurrence of typhoid fever followed by pellagra that true secondary pellagra in

typhoid was observed He also found cases when an intercurrent typhoid occurred during the course of pellagra Though somewhat similar cases had been reported by Landouzy (181) and Strambio (347), their nature is not clear Procopiu (150) and Watson (382) both observed the association of typhoid and pellagra though they regarded the typhoid as a complication Roberts (290) mentioned cases where typhoid was clearly the precipitating agent of pellagra Other cases are reported (13, 14, 152, 285, 396) It is interesting that since the therapy of typhoid fever has included proper feeding pellagra as a complication has not been reported in this country We have not seen a case

5 *Syphilis* It is improbable that early syphilis, except the congenital type, impairs nutrition On the other hand many of the destructive ravages of late syphilis are handicaps of the most severe kind These may vary from syphilis of the stomach to the benignant inertia and economic chaos of paresis, from the persistent food loss of tabetic gastric crises to the nutritional failure in congestive heart failure consequent upon luetic aortitis and aortic regurgitation Even most careful anti-luetic therapy may be marred by accidents such as hepatitis which interfere with the fine balances of metabolism and nutrition The high incidence of pellagra among syphilitics was repeatedly emphasized by Babes (13, 14) and has been noted by many workers (92, 150, 221, 230, 234, 280, 283) Much of this association is coincidental because both syphilis and malnutrition prevail among economically maladjusted and mentally retarded levels of society We have been struck, however, by the relative rarity of syphilis among the endemic pellagrins in Alabama When syphilis was a factor, alcoholism and other diseases were ancillary

We have seen pellagra develop in two victims of tabes when the loss of food from repeated vomiting was the prime causative factor Luetic aortitis with congestive failure and progressive liver enlargement was responsible in two instances Aneurysm with compression of the mediastinal structures and esophageal deformity was the background in another case From this evidence, and the literature cited, syphilis appears to be an important factor in nutritional failure only in the tertiary or destructive stages

6 *Leprosy* It is highly probable that pellagra and many other chronic affections of the skin were included under the term leprosy in the ancient past Casal (57) originally described pellagra as "a kind of leprosy, very strange" One of the synonyms for the disease in Spain was "Asturian leprosy" Pruner (277) originally wrote of pellagra in Egypt under the heading of "Leproses" In later times but before the modern period, it was generally taught that leprosy, pellagra and tuberculosis thrive in the presence of undernutrition R M Wilson (389, 390) in Korea was the first to report a series of lepers who developed pellagra as a complication Lowe (195) in India reported 40 cases of pellagra developing in a leper colony These people differed from the natives outside the colony only in the leprosy, so Lowe considered that leprosy was a true predisposing cause of pellagra Raman (279) also reported pellagra secondary to leprosy Many factors favor this complication (251) Chronic debilitating disease undermines nutrition Infection and trophic changes are important It is probable that

malnutrition predisposes to leprosy also We have had no experience with pellagra in leprosy

7 *Childhood diseases* The older pellagrologists did not write of the association of pellagra with childhood diseases and we owe the first observation to Rice (286, 287) In discussing pellagra in two South Carolina orphanages, he said, "in both orphanages an epidemic of measles and whooping cough occurred just prior to the outbreak of pellagra" Siler, Garrison and MacNeal (322) stated that "in a number of cases the development of pellagrous symptoms in children was preceded by one of the acute exanthematous diseases of childhood" Niles (246) mentioned cases following pertussis Kingery (174) saw a similar case, as did Greenfield and Holmes (130) who also observed pellagra following chicken pox and whooping cough We have found no mention of mumps or scarlet fever specifically as precipitating episodes (37) but we have seen 3 cases of pellagra following mumps The difficulty of ingesting food, the frequently upset stomach with ready vomiting and refusal to eat, all bear their weight in disturbing the normal nutritional balance It is probable that in regions of poor nutrition the acute infectious diseases of children are frequent causes of mild vitamin deficiency syndromes, but rarely of frank pellagra

8 Miscellaneous infections

(a) *Appendicitis* Niles (246) mentioned appendicitis occurring during the course of pellagra, though from the description it is probable that the difficulty with the appendix preceded the pellagra Other cases have been noted (90, 150)

(b) *Chronic bronchitis* Gemma (116) has described a fetid bronchitis in pellagrins and in some patients the advent of bronchitis was associated with an exacerbation of the pellagra in the late winter and spring There are other reports (13, 162, 387)

(c) *Gangrene of the lung and pulmonary abscess* Labus (179) was the first to record the occurrence of pellagra with gangrene of the lung Since that time a few isolated reports have appeared (173, 177, 351) Chronic pulmonary abscess or gangrene as the antecedent cause of pellagra has been noted (173, 177, 351)

(d) *Infected wounds* Sydenstricker (351) has seen pellagra follow severe wound infection

(e) *Influenza* Though Agostini (1), Roberts (290), Dyer (90) and Garrett (114) have observed pellagra developing during or after an attack of influenza the absence of any conspicuous increase in pellagra in the wake of the pandemic of 1917–20 indicates that the association is not very frequent

(f) *Otitis Media* Pellagra following chronic middle ear infections has been observed (274, 351)

(g) *Meningitis* A possible case of pellagra secondary to meningitis was discussed by Clark (62) Other cases have been recorded (343, 351)

(h) *Peritonitis* In addition to tuberculous peritonitis, pellagra following infection of the peritoneum has been mentioned (315, 332, 351)

(i) *Staphylococcal septicemia* Boggs and Padget (39) observed pellagra following staphylococcal septicemia with multiple abscesses

(j) *Tetanus* Labus (179) has reported pellagra in tetanus In such a case

lockjaw with its obstruction to the intake of solid food and the increased metabolism might readily precipitate the disease

(k) *Miscellaneous* Among the miscellaneous fevers and infections which may be complicated by pellagra, are found *furunculosis* and *puerperal fever* (193), *typhus* (179), *unexplained fever* and *pyelitis* (344), *brain abscess* (139, 181), *infected leg* (272), and *yellow fever* (138)

Certain febrile diseases are discussed under the body system involved Others may be found in Table V

VIII PREGNANCY AND LACTATION

The frequent outbreak of pellagra during pregnancy and lactation formerly was considered to be a result of "impaired vitality" It became intelligible when it was recognized that pellagra was a deficiency disease Though such terms as "nursing mothers' sore tongue" may indicate an ancient history the earliest recognition of pellagra following pregnancy was made by the elder Strambio (347) in 1786 Calderini (55) studied the incidence, age and sex distribution of pellagra by statistical methods, showing that the malady developed earlier and lasted longer in women than men In addition, more women had pellagra No reason was advanced for this discrepancy Brief note of pregnancy as a precursor of pellagra is to be found in records published by many observers (14, 41, 84, 290, 303, 309, 310)

The first comprehension of the probable reason for this unhappy result of pregnancy and lactation is found in Vedder's article written in 1914 (373) where he showed that the preponderance of pellagra in women during the childbearing period could be explained most readily on the basis of a dietary deficiency In this respect pellagra was analogous to beriberi where this unusual incidence was sometimes seen (372)

The first investigation of the relation of pregnancy and childbirth to pellagra was carried out by Siler, Garrison and MacNeal (322–324) They found that the initial attack of pellagra did not often follow immediately upon the termination of pregnancy, but attacks during the first six months after childbirth were numerous In their patients the incidence of pellagra *during pregnancy* was very low If recurrence came it was in the late months of pregnancy They noted a high incidence of pellagra when the last months of gestation coincided with the seasonal peak of pellagra in spring and early summer months. Unfortunately, they made no study of the number of previous pregnancies, and no mention of lactation, or abnormalities of the puerperium, though their figures show that it was the period of lactation rather than pregnancy itself, which was associated with the heightened incidence of pellagra They concluded that pellagra was an obscure infection

H F Harris (150) who believed pellagra was hereditary, did not consider that any of the collected figures gave evidence for true female preponderance of statistical worth on the grounds that dormant or subclinical pellagra was not recognized and thus never got into morbidity tables He did admit an influence of the puerperal state and nursing upon pellagra

Goldberger (120) emphasized the important part played by pregnancy, childbearing and lactation in predisposing to pellagra Guthrie (138) and Gregg (131) have mentioned the deleterious effect of lactation and pregnancy A special article on the subject was written by Crispolti (76) Stannus (343) believed that the reduction in gastric HCl during pregnancy favored the appearance of pellagra The development of pellagra during pregnancy and the period of lactation has been stressed by many writers (15, 16, 118, 142, 152, 178, 246, 272, 330, 337, 366)

Miscarriages as precipitating episodes have been mentioned (199, 290, 309, 310, 383)

Certain causes for the unfavorable influence of pregnancy, parturition and lactation upon nutrition are no longer obscure The fetus must derive its entire tissue substance from the mother This form of parasitism is no more benignant than that of any invading parasite Were no other factors at play the tissue building materials leeched from the mother during gestation constitute a severe

TABLE VI

Gynecological conditions

DISEASE OR CONDITION	CASES IN WHICH THE CONDITION WAS THE PRINCIPAL CAUSE			CASES IN WHICH IT WAS AN ACCESSORY CONTRIBUTING FACTOR	WHITE		COLORED		AVERAGE AGE
	Total	Ohio	Alabama		Female	Male	Female	Male	
Pregnancy and lactation	90	1	89	37+	89	—	1	—	30
Miscarriage	2	—	2	6	2	—	—	—	36
Myomata of uterus	1	—	1	7	—	—	1	—	39
Gonorrhea pelvic disease	4	3	1	11	1	—	3	—	35
Totals	97	4	93	61+	92	—	5	—	

loss Under circumstances of abundant health and optimum nutrition this loss is constantly replaced When diet is near the minimum in ordinarily required constituents the added strain of pregnancy may prove sufficient to undermine nutrition or even precipitate the full blown picture of vitamin deficiency disease Though the serious drain on calcium stores has long been recognized and appropriately remedied, the loss of water soluble vitamins and protein has been emphasized only recently Suboptimum supply of these factors may be as important as want of calcium in producing ill health as a result of pregnancy In addition, calcium deficiency, by destroying the integrity of the teeth, may be another source of ill nutrition caused by pregnancy Thus one deficiency may lead to another

Early in pregnancy nausea may interdict eating, or vomiting may prevent utilization of ingested food Often protein foods are distasteful and the diet bulks large in carbohydrates and less often in fats Curiosities of appetite and bizarre food fads are common The failure to eat wisely results in acceleration and accentuation of gastro intestinal disturbances because of the functions of the

B vitamins in normal alimentary activity. Thus an apparently innocuous minor complication of pregnancy may lead to a pernicious cycle ending in severe nutritional failure manifested by an outbreak of pellagra

The strain of childbirth, the worry and fears attendant thereto, the excessive muscular effort, severe fatigue, the use of anesthetics and sedatives, may lead to a crisis So also may the loss of blood and occurrence of varying degrees of infection add complications which make the early puerperium a time of election for pellagra Perhaps even the loss of materials forming the placenta is important

Lactation is but a continuation of the parasitism of pregnancy—changing from obligatory to facultative Under normal conditions the mammalian infant depends wholly on the mother's body for food This means that the erosion of never too ample vitamin reserves continues Because of nature's priority regulations it is usual for the mother to suffer rather than the nursing infant If the nutritional state is very poor with no reserve to fall back upon, the rapidly growing child may also develop signs of some specific deficiency (26, 337) Thus a secondary pellagra may occur in both nursing child and lactating mother In rare instances a nursing child may have clinical pellagra while the mother has no diagnostic evidence of it This may reflect a carry-over from an intrauterine deficiency in the fetus, a failure of normal lactation, some alimentary disorder impeding the infant's assimilation or unexplored factors

Recent studies with labelled molecules indicate that many essential constituents of the human organism are in a delicately balanced state of equilibrium with constant interchange between cell, tissue fluid and blood Continual loss of essential water soluble compounds through excretion must be replaced by a continual supply assimilated from food There appear to be inadequate barriers of renal threshold for many essential factors Mechanisms of homeostasis become progressively less efficient with the increasing availability of various essentials Absence of oxygen may prove fatal in minutes, of water in days, of energy foods in weeks, and of vitamins in longer periods Very little is known of storage depots of the B vitamins and enzymes in man, but studies with subjects on experimental diets show that the stores are readily exhausted, especially under circumstances imposing metabolic stress and strain (24, 335) It is small wonder that childbearing is a heavy drain upon natural stores of protoplasmic essentials—building materials, fuel supply and the enzymes releasing kinetic energy

Loss of vitamins may occur in any loss of body fluids or substance Several unmeasured processes may be of importance in the aggregate Women in the childbearing period are subject to the continually intermitting erosion of menstrual blood loss and often the depletions attending gestation and lactation The potential risks are more grave in those who have subsisted on diets just adequate to protect from vitamin deficiency For this reason the dangers in areas of endemic dietary deficiency are real whereas in regions of higher levels of subsistence the dangers are not so important

An attempt to determine the role of pregnancy among all patients with severe or moderately severe vitamin deficiency diseases in the Nutrition Clinic in

Birmingham for the years 1940 and 1941 has yielded some interesting figures The first group of selected patients so studied included 290 women (and 121 men) over 20 years of age All but 10 of the women had borne children and almost all had nursed them In 89 instances the relation of lactation and pregnancy was well established as the precipitating factor in pellagra, and it was probably a predisposing handicap in the majority In only 13% of the negro women were these factors of much importance, whereas in about 32% of the white women it was *the* important precipitating factor We confirmed the observation of Siler, Garrison and MacNeal that when the last trimester of pregnancy coincided with the seasonal peak of the pellagra an outbreak was most likely to occur It was further observed that the risk of relapse in pellagra was greater with each succeeding pregnancy and period of lactation As a corollary on this observation pellagra was more apt to occur in the younger than the older children and to be more severe In an area of endemic marginal nutrition families with a fixed income and fixed food supply will encounter more nutritional deficiency as the family grows larger because the meagre ration is spread thinner and thinner The mother in particular runs a greater risk of pellagra with a family increasing in size and food requirement Contrary to a widespread belief these pellagrins were remarkably fertile

A totally unexplored field is the relation of vitamins to endocrine function in women We have made observations which suggest that this should be investigated (24) A few hints of important relationships between vitamins and hormones are noted in the literature (150, 196, 309)

The accidents of pregnancy and the puerperium also have an unfavorable influence on nutrition In four of our patients the outbreak of pellagra followed an infected abortion Miscarriage twice and tubal pregnancy (with rupture) once were the direct precipitating agents Besides the usual factors, infection, hemorrhage and operation were important in these cases

IX PELVIC DISEASE IN WOMEN

Though many had noted the preponderance of females of the childbearing age among pellagrins no one stressed the possible cause and effect relationship of pelvic disease before Saunders (309, 310), who called attention to pelvic disease, abortion and gynecological operations as antecedents of pellagra She also reemphasized the frequent occurrence of menstrual and pelvic disorders during the course of pellagra Deeks (84) recorded an instance of pellagra complicating gonorrheal pelvic disease but made no comment upon it Siler, Garrison and MacNeal (321) stressed the increased likelihood of pellagra in women with pelvic disease, emphasizing its general depressing influence Garrett (114) observed one patient with gonorrheal pelvic disease and uterine myomata who developed pellagra One of Hudson's (164) patients developed pellagra following an operation for pelvic inflammatory disease Turner (365) mentioned similar cases A very large series of pellagrins with this disorder was reported by Crutchfield (77) An operation for pelvic gonorrhea resulting in a fecal fistula which eventuated in pellagra was reported by Davies and McGregor (81) Pelvic disease was noted

by Sydenstricker and Armstrong (351) in 3% of their pellagrins The mechanisms involved were not discussed in any of these cases Chronic infection, pain, fever, loss of appetite seem to be important

Chronic pelvic inflammation definitely undermined the health and nutrition in 15 of our patients who developed pellagra Twelve were colored The average age was 35 The sequels of improperly treated gonorrhea in the female include many conditions favoring chronic ill health Arthritis, perihepatitis, pelvic adhesions with partial bowel obstruction as well as the infection itself may all add a burden which finally disturbs nutrition to the point of clinical deficiency disease

Carcinoma of the uterus The disastrous nutritional consequences of any generalized neoplastic disease are well known Instances of pellagra following carcinoma of the cervix or body of the uterus are known (119, 164, 313) The rôle of surgical operation and radiotherapy must be considered In three of our patients carcinoma of the cervix and its complications led to pellagra

X NEOPLASTIC DISEASES

Several mechanisms may be involved in the development of pellagra as a complication of neoplasms Some of these relationships are discussed elsewhere The following points are considered here

1 *Metabolism* It is well known that the metabolic requirements of rapidly growing tissue are high If the neoplastic tissue mass is small in comparison with that of the host, this added demand may be met without serious depletion of the host In very malignant tumors, invasion and mestastasis rapidly increase the total mass of the tumor in relation to that of the body As far as the quantitative aspect of metabolic requirement, it is apparent that a tumor is a more serious parasite when large or when very malignant than when small or slowly growing Consequently a deficiency disease is apt to appear late in the course of neoplastic disease and the risk is worse with very malignant tumors It has not been demonstrated that the parasitism of a tumor is ever the sole agent in producing a deficiency syndrome The hope of treating tumors by creating a deficiency in the host which starves the tumor seems remote because the host probably would die first

2 *Mechanical obstacles to nutrition* Neoplasms in or near the alimentary canal may result in mechanical as well as functional disorders of digestion A tumor of the tongue, lip, jaw or gullet may interfere with biting, chewing or swallowing by reason of disordered mechanics, pain or a loss of appetite The sequelae of obstruction at different levels of the gut have been discussed Inevitably there is an acute nutritional imbalance Development of objective manifestations of deficiency disease depends in large part upon the state of nutrition at the time obstruction becomes complete and upon the possibility of by-passing it Neoplastic diseases of the colon are associated with varying disturbances in bowel function Alternating diarrhea and constipation are frequently encountered Cathartics may be abused in an attempt to overcome constipation Nausea and vomiting put further restrictions on food available for digestion

3 *Infection* Neoplasms may become the nidus of bacterial infection An increase in metabolism may be expected with the concomitant rise in temperature Tissue necrosis which results from ischemia in some tumors may produce similar disturbances

4 *Hemorrhage* from various tumors may be acute or chronic, large or small In some instances severe anemia results This interferes with nutrition in the widest sense and may combine with other factors to facilitate the development of vitamin deficiency

5 *Radiation therapy* It is well known that radiation of some normal or neoplastic tissues may be followed by nausea, vomiting, headache and loss of appetite Radiation sickness is in itself a hindrance to nutrition It is possible that another mechanism may exist in the disturbance of respiratory enzyme systems (25)

6 *Dextrose* Dextrose as a food has the same defect as alcohol It supplies calories in an accessible form but contains no vitamins to help in combustion

The final stage of many neoplastic diseases is cachexia This represents failure in nutrition plus the harm done by "toxic" factors Why pellagra is not more frequent in such states is not clear Pellagra does not occur in complete starvation When all food is withheld and energy is derived from the breakdown of body tissues death occurs before vitamin deficiencies are manifest in clinical form The total metabolism is greatly reduced in starvation and activity is restricted voluntarily Cellular breakdown may mobilize vitamins from storage or liberate enzymes from autolyzed cells in quantities sufficient to protect the remaining tissues against severe degrees of deficiency as long as the metabolic requirements are very low

Though Strambio (347) mentioned it, Landouzy (181) was the first to stress the occurrence of pellagra in persons afflicted with various cancerous processes Specific carcinomas include prostate, pelvis (77), pancreas (241, 313), penis (279) Other neoplasms are considered under the body system involved Writers on sporadic pellagra have noted the emergence of pellagra in many cachectic conditions The problem was confused by the maize doctrinaires who would admit no pellagra without corn and who added confusion with their tortured arguments to get around the difficulties thus engendered, by inventing specious terms such as pseudo pellagra and parapellagra The relationship of nutrition to neoplastic growth is still not well understood and offers a fertile field for study

XI ENDOCRINE DISORDERS

Our knowledge of interrelationships among vitamins, enzymes and hormones rests upon a poorly integrated accumulation of fragmentary and sometimes conflicting and irrelevant observations made on sundry micro organisms, experimental animals and human beings The complexity of the problem becomes manifest when one tries to correlate polyglandular endocrine dyscrasias with multiple vitamin deficiencies The question has been raised does an inadequate supply of vitamins ever give rise to a specific endocrine disease? Does the converse proposition hold? Is the inordinately large number of females of child-

bearing age among endemic pellagrins a consequence of some subtle endocrine disorder, connected with the tides of estrogen ebb and flow or of pituitary function, in addition to the better understood vitamin depletion caused by menstruation, childbearing and lactation? McCarrison (198) and others have noted changes in the thyroid and adrenals of experimental animals fed on a vitamin B deficient diet No such study has been reported since the more recently distinguished factors of the B complex have been made available The effects of inanition alone are well known and the similarity between Simmonds' disease and anorexia nervosa suggest a secondary rather than primary pituitary disorder in malnutrition Nauck (243) was impressed by a possible pituitary deficiency in pellagra and a recent study of pituitary gland therapy in "pellagra" may indicate a relationship between the pituitary gland and utilization of nicotinic acid and riboflavin In the cases reported by Sutton and Ashworth (152) it is not possible to evaluate diarrhea, failure of absorption, high requirement and physical activity They made no effort to establish the presence of a deficiency by laboratory methods Diet does not appear to have been controlled The development of signs of riboflavin deficiency during intensive nicotinic acid therapy is not rare (354) The most that can be said is that more cases adequately controlled should be studied before drawing conclusions

Aldalli (2), Roberts (290), Harris (150) and Kooser and Blankenhorn (178) have emphasized the high incidence of pellagra during the menopause It is not possible to appraise the rôle of hormonal readjustments, psychic aberrations, poor diet and other factors in menopausal disorders In different patients entirely different factors seem to operate We have been impressed by the history of the well nigh uninterrupted chain of pregnancy, parturition and lactation in our patients who develop diagnostic evidence of pellagra during the menopause More specific factors cannot be evaluated

Sandwith (304) has mentioned puberty in boys as a predisposing cause of pellagra From unpublished studies (24) it is apparent that there is a sparing action if anything since the incidence of pellagra is very low among persons from 10 to 20 years of age We have seen pellagra occur following a sudden spurt of growth in adolescence Cid Rojas (62) has mentioned pellagra complicating renal rickets Endocrine problems in relation to pellagra are dealt with by Aschoff (11), deLangen (182), Thannhauser (356) and Mainzer (212, 213, 214)

1 *Diabetes insipidus* Any distortion of the normal fluid-electrolyte balance giving rise to persistent polyuria conceivably might lead to such an increased excretion of water-soluble vitamins or enzymes as to produce a deficiency disease syndrome In the absence of specific information regarding threshold and normal daily excretion this possible cause of deficiency remains hypothetical There are only two references to pellagra in diabetes insipidus The first is that of Hameau (144) who mentioned, in his Paris Thesis, a case of pellagra with extreme polyuria, in all probability diabetes insipidus Vogt-Møller (379) reported a patient with diabetes insipidus who developed typical signs of mild pellagra The vitamin balance in man has not been studied in induced diuresis since tests for vitamin B-complex factors have become available In this connection it is of interest that

the Russian worker Rassulev (281) considered diabetes insipidus to be one of the constant features of pellagra His evidence is not clear but he did report pellagra in the presence of extreme polyuria and polydipsia Cowgill, Rosenberg and Rogoff (72) demonstrated the accelerating power of enforced diuresis on the development of signs of vitamin B_1 deficiency in dogs It seems probable that forcing fluids too assiduously is partly responsible for some cases of postoperative pellagra (354, 366)

2 *Diabetes mellitus* That full blown pellagra is a rare complication of diabetes mellitus is apparent from the surveyed literature on pellagra in the pre-nicotinic acid days (12, 38, 223, 247, 290, 323, 351, 392) The occurrence of glossitis and stomatitis in diabetics, however, had been noted for many years (336, 391) Harris (152) observed pellagra in less than a tenth of 1% of a large series of diabetics Vilter, Vilter and Spies (376), observing a decrease in the concentration of the codehydrogenases I and II in the blood of diabetics in severe acidosis, suggested a possible reason for the occasional association Our records contain four cases where pellagra developed as a complication of severe diabetes Sydenstricker, Geeslin and Weaver (353) and others (274, 379, 398) have observed this train of events They believe that sudden increments in carbohydrate or insulin putting an added burden on enzyme systems may precipitate the acute manifestations of pellagra It is important to recall the frequent association of infections in severe phases of diabetes and their auxiliary role in pellagra A similar pathogenesis for the peripheral neuritis long recognized in diabetes has been advanced (105) Hou (162) mentioned pellagra associated with renal glycosuria

Pellagra may arise as a complication of diabetes for several reasons The high carbohydrate diet often prescribed may be deficient in protein and vitamins This is especially true when sugars and highly milled grains and their products constitute the great bulk of the caloric supply The part of infection has been noted Because of the continued polyuria water-soluble vitamins and their related enzymes may be washed out in the urine though it has not been demonstrated that vitamins are lost in dangerous amounts in the polyuria of diabetes The decrease in nicotinic acid amide containing nucleotides in diabetic coma does not occur in well regulated diabetics

3 *Thyroid disease* Recognition of endemic goitre as a deficiency disease was one of the early clear cut demonstrations of the positive harm done by a negative force in nutrition An association of pellagra and thyroid disease was recognized long ago by Lombroso (193) It was his impression that certain forms of thyroid disease resulted from the same corn "toxins" that produced pellagra From his case records, however, it is apparent that the thyroid disorder antedated the pellagra In Lombardy the association of cretinism and pellagra was commonplace but it was generally believed that both were manifestations of corn poisoning or that cretinism was an inherited masquerade of pellagra Valtorta (370) made an extensive study of the thyroid in pellagra and he concluded that the insanity of pellagra was often the cause of "dysthyroidism" which might assume the guise of either over- or under-activity H F Harris (150) cited experimental evidence on dogs kept on a corn diet for a short time in which profound alterations

of the thyroid gland were found After these early observations there was a period during which the polemics concerning etiology of pellagra were so active that many auxiliary factors in the cause were used only as starting points for some new hypothesis

Babes (13) implied that pellagra might be a sequel rather than a cause of thyroid disease In a series of 250 cases published in 1912 he found cretinism had existed in 25 and goitre in 32 cases He was impressed with the multiplicity of factors impairing general health which tended to produce pellagra Niles (246) also mentioned thyroid disease as an associated factor In more recent years Shelly (317) has observed pellagra in association with thyroid disturbances

Assuming that the essential deficiency operating in the genesis of pellagra is a failure in the catalytic chain of tissue oxidations, acceleration of tissue respiration such as obtains in hyperactivity of the thyroid gland might result in the biochemical lesion responsible for the ultimate emergence of clinical pellagra That pellagra is not an almost constant sequel of thyrotoxicosis may indicate that the qualitative as well as quantitative increase in diet ordinarily is able to supply the increased requirement for enzyme precursors found in food When the diet is poor in nicotinic acid but more nearly adequate for caloric demands pellagra may result It may also be of importance that powers of intestinal absorption are enhanced during increased thyroid activity (10) The nutritional disasters which may result from the qualitative failure in nutrition when carbohydrate is increased without vitamins have been observed (141, 366)

In cretinism and myxedema pellagra may occur but because of another set of circumstances One would expect upon theoretical grounds that the reduced total metabolism in hypothyroidism would render the victim relatively impervious to pellagra This is counter-balanced by defective absorptive powers (10) and by voluntary dietary restrictions which may occur in myxedema Besides the early cases (13, 193, 333), no note of pellagra in myxedema was made until Greene's report (129) From his histories and therapeutic studies it is probable that myxedema was the primary disorder and that pellagra was a sequel It was not possible to say that improper diet rather than reduced absorption from the alimentary canal was not of major etiological importance in these cases A similar case was reported by van Bogaert (38)

We have observed instances of very mild pellagra complicating thyrotoxicosis This is usually controlled well enough by rest and iodine but in all cases the course is made smoother by proper vitamin and diet therapy In two pellagrins thyroid overactivity was clearly responsible for the outbreak of severe pellagra. In one, response to nicotinic acid was dramatic and in the other a remission followed "lugolization" and subtotal thyroidectomy. We have seen pellagra develop in one untreated patient with myxedema In another, relapse occurred during the thyroid administration

In an experiment one of us (W B B) conducted upon a group of 89 ambulatory patients in Birmingham in 1910 during a stage when their pellagra was quiescent, administration of 3–6 grains of thyroid substance daily for 4–8 weeks was followed by relapse in only a few more instances than in a control group All those who

relapsed had diarrhea before the dermal and mucosal signs of pellagra reappeared It was not possible to control this study with satisfactory estimates of basal metabolism

4 *Addison's disease* The connection between pellagra and Addison's disease is unique because of many similar clinical features Years ago it was recognized that the differential diagnosis might be impossible in those cases where the manifestations of Addison's disease merged imperceptibly into those of pellagra, or vice versa Neusser (244) was the first to comment upon the similar disturbances in the two diseases He emphasized the extreme changes to be found in blondes It was hoped that by analogy with Addison's disease some light would be thrown on the obscure cause of pellagra Finotti and Tedeschi (110) reported abnormalities in the adrenals in pellagrins Rubinato (297) called attention to the hypotension, asthenia, hypothermia and pigmentation in a pellagrin whose adrenals showed fibrous atrophy In retrospect it appears that the Addison's syndrome was the initial disturbance and the pellagra a sequel though the author interpreted it otherwise Rondoni and Montagnani (295) claimed to have produced changes in the adrenals of animals on a corn diet McCarrison (198) reported extensive endocrine gland changes in various animals on diets poor in the B vitamins and was particularly impressed by the adrenal hypertrophy of pigeons and monkeys It seems that Thannhauser's (356) case was the first instance where it was clearly recognized that the adrenal disease anteceded clinical signs of pellagra The autopsy of this case was reported in detail by Aschoff (11) Packard and Wechsler (258) reported adrenal insufficiency in 4 subjects with chronic malnutrition Levy Simpson (188) reviewed the literature on this interesting problem and emphasized the dual relationship between pellagra and Addison's disease Sclare (311) reported a case with symptoms of adrenal hypofunction but apparently normal adrenals at autopsy A further report on the problem is that of Rabinovich and Kogan (278)

In typical cases the pigmentary changes in the two diseases are easily distinguished In Addison's disease the pigmentation tends to be an accentuation of the normal It is generalized It appears in the mucous membranes and in the palmar folds In pellagra the pigment appears where there has been a dermal lesion The changes are localized and sharply outlined, symmetrical and appear in regions exposed to irritation or trauma Very rarely pigmentation may be diffuse and resemble that in Addison's disease but does not appear in the mucous membranes or skin folds

We have observed pellagra complicating Addison's disease in four instances Loss of appetite, nausea, and abdominal cramps all reduced the food intake, and with the advent of vomiting and diarrhea, clinical signs of pellagra developed Althausen (10) has reported that intestinal absorption is defective in adrenal disease Whether this is primary or secondary is not known It is not possible from the scanty information to know whether phosphorylation defects are of importance in disturbing nutrition further

Calvo Melendro and Alongo (56) have reported adrenal tumor and pellagra

XII RENAL DISEASE

To judge from the reports, pellagra is an uncommon sequel of renal disease A few early European pellagrologists considered chronic nephritis a *result* of pellagra (117, 222) In our experience many patients with renal disease, particularly the chronic types associated with hypertension and heart failure, ultimately developed pellagra Deeks (84) gave case reports of pellagra complicating nephritis, both acute and chronic, and Martin (224) likewise mentioned chronic nephritis Boggs and Padget (39) observed chronic nephritis in two of their pellagrins (6 5%) but Sydenstricker and Armstrong (351) found chronic nephritis in less than 1% of their cases Smith and Stevens (329) emphasized the role of cardio-vascular-renal disease in pellagra in California Haden and Matthews have reported similar cases in an endemic region Goldbloom and Lieberson (121) gave a detailed case report of pellagra in a cardionephritic and discussed the nature of this complication There are others reported (141, 226) We have seen pellagra complicate pyelonephritis four times, nephrosclerosis with hypertension and uremia four times, amyloid nephrosis (tuberculosis) and glomerulonephritis once each The occurrence of nausea, vomiting and headache reduced food intake considerably and the economic calamity of invalidism reduced the ability to procure food Conceivably the loss of protein in the urine may have removed the essential protein . On *a priori* grounds one might suspect that the renal failure of nephritis would cause retention of water soluble vitamins paralleling the retention of non-protein nitrogen This would be the physiological converse of diabetes insipidus There is no evidence for this If it occurs it is more than counterbalanced by other factors

Stannus (343) has reported pellagra accompanying pyelitis with B coli bacilluria Walsh and Norton (381) have discussed pellagra complicating nephrolithiasis

XIII CONGESTIVE HEART FAILURE

Hypertension No special studies of pellagra as a sequel of hypertension and heart failure have been found in the literature surveyed Cases where such an influence may have been operative have been reported without comment (137, 176, 227, 302, 303)

In our own experience the frequency of pellagra as a complication of hypertension and congestive heart failure has been impressive The Ohio group is represented heavily (see Table VII) The preponderance of colored females is extreme Average ages are given in the chart It is noteworthy that in all patients of this group there were several complicating factors impairing nutrition Alcoholism was frequent, cirrhosis either "alcoholic" or "cardiac" occurred Digitalis intoxication occurred 5 times and the distressing vomiting was related to the precipitation of pellagra in 2 cases Diabetes mellitus occurred Uremia was frequent Addiction to morphine was seen also Unexplained fever, chronic bronchitis and pneumonia occurred Myocardial infarction and pulmonary infarction and embolic phenomena were encountered in rare instances

We did not observe a single instance of pellagra secondary to hypertension and

heart failure in the Alabama group We have been impressed by the rarity of incapacitating forms of arteriosclerosis and the apparent benignity of the rather uncommon hypertension among the endemic pellagrins in Alabama (24) In this connection O'Leary's (187) observation of the rarity of arteriosclerosis in alcoholic cirrhosis of the liver is interesting

Other forms of heart failure We have seen pellagra complicate acute exacerbations of rheumatic fever with severe valvular disease and congestive failure three times This has been observed by others (241, 302, 351, 397) In one case of luetic aortitis with aortic regurgitation and heart failure pellagra followed a period of vomiting thought to have resulted from overdigitalization In one patient with subacute bacterial endocarditis pellagra appeared terminally

TABLE VII

Heart disease

DISEASE OR CONDITION	CASES IN WHICH THE CONDITION WAS THE PRINCIPAL CAUSE			CASES IN WHICH IT WAS AN ACCESSORY CONTRIBUTING FACTOR	WHITE		COLORED		AVERAGE AGE
	Total	Ohio	Alabama		Female	Male	Female	Male	
Hypertension, heart failure, coronary artery disease (myocardial infarction 2, digitalis poisoning 2)	19	15	4	7	2	6	7	4	59
Cardio-vascular-renal disease, uremia, generalized arteriosclerosis	5	5	—	7	—	2	3	—	57
Rheumatic heart disease with failure (sub-acute bacterial endocarditis 1)	5	4	1	1	1	1	3	—	40
Syphilitic aortitis with regurgitation and failure	3	3	—	—	—	1	1	1	50
Totals	32	27	5	15	3	10	14	5	

Discussion It seems probable that the mechanisms causing the development of pellagra in congestive failure are multiple First of all food intake is reduced This may be an economic misfortune resulting from invalidism More often it follows voluntary restriction of diet because of anorexia, pain, nausea, or loss by vomiting and diarrhea Ill advised restriction may be part of the therapeutic regimen Congestive failure is associated with an increase in metabolism, presumably arising from the increased work needed for the rapid and difficult breathing Anoxemia and tissue anoxia reduce the availability of oxygen, and might produce changes similar to those occurring from a specific enzyme deficiency There is no evidence, however, that the chronic reduced oxygen tension of high altitudes is a precursor of pellagra

The following case illustrates the complicated clinical background which may be found in pellagra secondary to heart disease

Case report M W, (U 109525) This 39-year-old childless colored woman was admitted to the medical service of the Cincinnati General Hospital on December 14, 1938, severely incapacitated by rheumatic heart disease and congestive failure Her family history was not relevant As a child she had repeated attacks of "quinsy sore throat" At the age of 15 she had a prostrating attack of acute migratory polyarthritis which kept her in bed for three months There were no other severe bouts of rheumatism Two years before entry she became aware of gradually increasing shortness of breath Ankle edema occurred regularly in the evening These symptoms progressed insidiously so that a year before admission she was obliged to give up her work as a laundress Weakness and dyspnea would force her to rest in bed for short periods At about this time she began restricting her diet because of post-prandial fullness There was no story of alcohol addiction Almost no meat was eaten, but bread, soups, or soft drinks, and other largely carbohydrate foods constituted the bulk of her restricted diet There was an increase in her usual constipation She took tablets of digitalis according to her whim and there were several spells of vomiting which may have resulted from too enthusiastic dosage Throughout the month before she came in she was confined to her bed but took no digitalis In spite of this rest, orthopnea, paroxysmal dyspnea at night and massive edema increased and she was admitted to the hospital in great distress She had not noticed the signs of pellagra which were apparent upon admission

Physical examination revealed a desperately orthopneic, waterlogged colored woman Temperature was 101°F, pulse 110 (with a deficit of 20) and respirations 30 to the minute Arterial blood pressure was 110/80 mm of Hg The neck veins were engorged Her abdomen was distended but she did not admit having any pain There were several irregular pigmented areas in the skin Typical pellagrous dermatitis was found on her feet, legs and elbows, and less characteristic skin changes in her hands and face The teeth were carious and there was much foul debris in the mouth The tongue was scalloped with indentations from the teeth At the tip and along the margins there was a fiery erythema and smoothness from edema The heart was enormously enlarged to the right and left In the mid axillary line on the left the point of maximum impulse could be seen and felt There was a systolic apical murmur and a soft rumbling diastolic murmur as well as a diastolic thrill in the fourth intercostal space immediately to the right of the sternum The liver was felt 5 centimeters below the costal margin Massive edema of the lower half of the body was noted and there were areas of paraesthesia in the skin Laboratory findings included a leucocyte count of 16,000 and erythrocyte count of 5 9 million per cubic millimeter The urine obtained by catheter contained large amounts of albumen, a few white cells and casts Urinary pigments were found in abnormally high amounts by the B E S (29) technique Several blood cultures were sterile The Kahn reaction was positive The electrocardiogram confirmed the clinical diagnosis of auricular fibrillation and showed a tendency to right axis deviation and very low voltage of the T waves

Course The patient was digitalized and given diuretics Fifty milligrams of thiamine were injected twice daily and vitamin C in doses of 50 mg was given orally Nicotinic acid was given by mouth in 5 doses of 100 mg daily The only response was a rather dramatic improvement in the tongue which lost its fiery red color and edema In spite of all supportive measures the patient died from increasing congestive heart failure after five days in the hospital

Post-mortem findings The dilated and hypertrophied heart weighed 575 grams, including a large thrombus in the left auricle and a smaller one in the right There was advanced stenosis of the mitral valve through which the index finger could not pass There were several infarcts in the lungs Bilateral hydrothorax and ascites gave evidence of passive congestion of the viscera, which was also prominent in the liver Edema and congestive changes appeared throughout most of the gut The adrenals and other organs presented nothing of note

Discussion This patient is representative of the group developing pellagra as a consequence of cardiac failure As a primary reason one must count the

restriction of diet and poor selection of protective foods Even if we discount the poverty resulting from a loss of steady work, there are many malign influences interfering with adequate nutrition The loss of appetite was of importance Nausea and vomiting contributed The processes of digestion itself probably were impeded by the severe congestion and edema of the gut so that secretion of digestive enzymes, normal motility, and absorption were reduced Many functions of the engorged, fibrotic liver undoubtedly were far from optimum In addition to these barriers to proper ingress of foods metabolism was elevated Fever in association with bronchopneumonia and perhaps rheumatic infection added another stress Finally the generalized anoxemia contributed its insult Thus there was a conjunction of conditions increasing the need for tissue respiration with a series of barriers to the assimilation of essential dietary factors

XIV ROENTGEN THERAPY

The first specific report of pellagra following radiotherapy was that of Rattner (282) in 1935 His patient had heavy radiation over the lower abdomen for an ovarian carcinoma This was followed by severe Roentgen sickness with extreme anorexia, nausea and vomiting Typical pellagra developed It cleared up when the gastro-intestinal tract returned to a normal state and food was retained Davies and McGregor (81) reported pellagra in a 43-year-old woman with menopausal symptoms in whom treatment of menorrhagia with radium was followed by pellagra Bean, Vilter and Spies (25) demonstrated that radiation over the upper abdomen was followed by a temporary fall in the pyridine coenzymes I and II in the blood Frequently pigments appeared in the urine similar to those excreted by pellagrins (29) The hypothesis was advanced that X-ray therapy might regularly depress a number of the oxidation-reduction enzyme systems Recently, Dale (78) has reported evidence of *in vitro* inactivation of other enzymes by radiation Harris (152) reported pellagra developing in a woman given Roentgen therapy for mediastinal Hodgkin's disease The signs and symptoms of pellagra were relieved by liver therapy Sydenstricker (354) related an interesting example where pellagra followed radiation, dermatitis localizing in the exposed skin

We have observed 5 patients in whom radiotherapy was followed by the development of pellagra In 3 radiation was used because of excessive bleeding from the uterus at the menopause Severe nausea and vomiting occurred and pellagra complicated the picture In another case X-ray and radium were used for carcinoma of the cervix and a severe chronic diarrhea resulted which eventuated in pellagra A similar case has occurred with early pellagrous lesions in a woman with radiotherapy for abdominal carcinomatosis (119)

Two possible mechanisms must be considered One is a depression of specific pyridine enzyme systems (25, 125) The second factor is the disturbed function and sometimes structure of the gut reported by Golden (122), Wallace (380) and others Diarrhea, vomiting and loss of appetite all favor nutritional disorders In addition persons receiving radiotherapy ordinarily have some severe disease for which it is administered The underlying condition may well pre-

dispose to pellagra with a long period of vitamin depletion before radiation precipitates the acute outbreak

Unpublished work by two of us (24) has revealed that X-ray sickness is readily produced by irradiation of the upper abdomen in undernourished persons kept on a diet poor in B-complex vitamins The same procedure in well fed controls did not cause sickness When the poorly fed subjects were saturated with thiamine or nicotinic acid for several days prior to a later identical exposure to X-ray the syndrome of Roentgen sickness was prevented or its severity reduced These studies are being extended

XV ANEMIA AND HEMORRHAGE

For more than a hundred years it has been recognized that anemia and pellagra may be found together Strambio (347) seems to have been the first to notice it Calderini (55) emphasized the frequent concurrence of chlorosis and pellagra in young women Labus (179) was impressed by severe hemorrhage leading to pellagra even in the age when bloodletting, the cloak for therapeutic ignorance, was panacea Strambio and Calderini both saw pellagra flare up after intemperate venesection In somewhat later studies it was recognized that anemia was often a sequel to pellagra or perhaps a symptom of the late stages of the condition (158, 163) The use of iron therapy in pellagra speaks for the presence of an associated iron deficiency anemia in some cases (35)

Only in the recent period has the relationship of deficiency diseases to anemia been placed on a sound footing Indeed, present concepts put some anemias in the category of deficiency diseases A review of the usual blood picture in pellagra may be found in the papers of Huck (163) and Spies and Chinn (339) The latter authors found that mild anemia with a tendency to macrocytosis was frequent, but any type of anemia might occur

Concerning anemia as a precursor of pellagra the data are not clear Acute blood loss was mentioned early (55, 347) We have seen a few cases where it seemed to be a precipitating agent In one the anemia was so severe that the erythematous glossitis was not recognized till after a transfusion had raised the hemoglobin level to 25 per cent of normal Although we have emphasized the diagnostic value of the lingual and buccal changes in pellagra (336), there are several questions still puzzling us The significance of the scalloped tongue with indentations from the teeth is not clear It indicates lingual edema but certainly may be seen in persons with no stigma of deficiency disease and in them does not respond to protracted vitamin therapy A study of the papillae with a hand lens which magnifies 20 times is more satisfactory than the slit lamp for at higher magnifications the field is too elusive and any attempt to steady the tongue produces artefacts which are very confusing The smooth fiery red tongue of acute pellagra has its papillae intact but they are obliterated by the edema so that the surface indeed is very slick In chronic pellagra, true atrophy occurs The redness may indicate a dilatation of the small arteries and arterioles (as in the erythematous skin) or it may result from a change in refraction in the swollen superficial epithelium The rapidity of the return to normal suggests that the change is primarily vascular

The Egyptian workers have emphasized the association of schistosomiasis and its attendant anemia as a cause of pellagra Biggam and Ghalioungui (35) recommended iron therapy in such cases Ellinger, Hassan and Taha (93) have made confirmatory observations

Similarities between pellagra and pernicious anemia have been noted for a long time Spies (339) showed that intrinsic factor failure was not usual in pellagra Newer studies on vitamin B complex factors have demonstrated that none of the fractions now known is the long sought extrinsic factor, which invalidates the early suggestion of Castle that this material might be vitamin B_{12}, though undoubtedly it is closely associated with it in natural sources

Mollow (231), Haden (141) and Harris (152) have seen pernicious anemia and pellagra in the same patient While it is possible that the pellagra developed as a sequel, it seems more probable that they were coincidental Recent studies by Moore, Vilter and Spies (232) have demonstrated that certain pellagrins with free HCl and intrinsic factor in the gastric juice, who have subsisted for long periods upon a diet very low or completely wanting in the extrinsic factor, develop a macrocytic anemia identical morphologically with Addisonian pernicious anemia We have seen patients with pernicious anemia who develop pellagra, perhaps more from changes in alimentary function (atrophy, achylia) than lack of nicotinic acid in the diet

We conclude that pellagra may occur in pernicious anemia, and that any severe anemia is apt to increase the severity of pellagra Acute hemorrhage may even precipitate it We do not know whether this influence is exerted because the blood cannot carry or store enough respiratory coenzymes or whether the nonspecific depressing influence is a sufficient handicap

Sydenstricker (350) has observed pellagra in a patient with sicklemia

XVI DRUGS AND CHEMICALS

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concoction as a specific in the treatment of pellagra in the past it is improbable that the misuse of drugs is a frequent precipitating agent

Reports of an antagonistic action of nicotinic acid and certain sulfa drugs in man and animals led us to investigate this question (24) Coenzyme determinations were carried out using the technique of Vilter, Vilter and Spies (376, 377) Five patients with pneumonia and seven with pyelitis of pregnancy treated with sulfapyridine were studied before, during and after symptoms of toxicity occurred They were all given nicotinic acid or its amide in doses of 100 mg three times daily In only one was there any improvement of manifestations of toxicity following nicotinic acid treatment This was a pregnant woman who had nausea and vomiting before she developed pyelitis, and whose diet was never very good Her blood cozymase level was low She might have been benefited by nicotinic acid regardless of the sulfapyridine reaction There were some patients who got worse after nicotinic acid The failure to find any therapeutic virtue in nicotinic acid under these conditions was so clear-cut that we discontinued the study

Approaching the question from another angle 11 ambulatory pellagrins were given sulfathiazole for periods of 8 weeks The lesions continued their usual course, all but one clearing up There was no indication of a tendency to precocious relapse, and no failure to respond to specific anti-pellagra therapy (24)

Finally pyridine-3-sulfonic acid, which is related to nicotinic acid in the same way as sulfanilamide is to para-amino-benzoic acid, was given for a two-week period to three persons with subclinical pellagra on a vitamin B "free" diet It was thought that it might antagonize some function of nicotoinic acid and thus accelerate the development of pellagra No such result was obtained Further studies with larger doses (more than 100 mg daily intravenously) and for longer periods are needed before drawing conclusions (24)

1 *Tobacco* Though it has been hinted that tobacco might supply nicotinic acid and thus tend to prevent pellagra, there is no evidence that tobacco is of any value in this direction A large proportion of pellagrins in the Nutrition Clinic in Alabama use tobacco in some form—snuff, chewing tobacco, cigarettes, pipes or cigars They are neither more nor less liable to pellagra than their fellows who do not use tobacco It is recognized by many that smoking reduces appetite and this interferes with nutrition in varying degrees Gillespie (118) has reported pellagra developing in a man who smoked excessively It is impossible to be certain that excessive smoking was not a manifestation of the nervousness of subclinical pellagra rather than its cause

2 *Narcotics* An early reference to morphine and narcotic addiction influencing the development of pellagra was made by Siler, Garrison and MacNeal (321, 323) Roberts (291) reported pellagra in morphine addicts and Guthrie (139) noted habituation to morphine, paregoric and bromides Hashish addiction was mentioned by Sandwith (304, 305) and Marie (221) Much caution is advisable in interpreting the relationship of pellagra and drug addiction We have seen a few victims tortured by the progressive complaints of nascent pellagra, who resorted to morphine This was followed by the outbreak of clinical

pellagra In such instances the morphine addiction was a reaction to or symptom of incipient pellagra though perhaps also the agent precipitating the disease in recognizable form The appetite and other gastro-intestinal functions may be severely disturbed Habituation to morphine in an adequately nourished person might reduce his intake of food and thus be an indirect cause of pellagra

It is possible that some narcotics may have a specific action in producing pellagra It is known that "dehydrogenases are inhibited by narcotics" (93) Perhaps some interference with cellular metabolism occurs following large doses of morphine though this has not been studied in man Certainly one might believe the reduced metabolism in morphinism would reduce the likelihood of pellagra

We have observed pellagra in two morphine addicts and once in a paraldehyde addict Mild cases of glossitis have been seen complicating bromide intoxication

XVII MISCELLANEOUS

1 *Snake bite* Among the bizarre precipitating agents in pellagra, the mention of snake bite must be made In natives of the Sudan Corkhill (68, 69) reported two instances of pellagra following a bite by a venomous snake Without knowledge of the effect of snake venom on tissue respiration the nature of this phenomenon cannot be stated It is possible that some specific inhibition of enzyme systems was responsible The fever, anorexia and other systemic disturbances may have been more important Of interest is the demonstration by Chain (60) that coenzyme I is inactivated by a nucleotidase from the venom of the black tiger snake

2 *Mosquito bite* Harris (150) has mentioned this as a rare forerunner of pellagra and Plunkett (272) has also noted it in a patient with an infected mosquito bite That it was more than circumstantial seems incredible

3 *Trauma* There are occasional remarks in the publications of European students on the development of pellagra following trauma (150, 302) Barthelemy and Onfrey (21) observed a case following fracture of the leg In persons we have seen where pellagra was first manifest or relapsed after injury, the fever, failure to eat, injections of quantities of parenteral dextrose, and hemorrhage seemed more important

4 *Asthma* The occurrence of pellagra as a sequel of bronchial asthma has been reported by Kooser and Blankenhorn (178) and Sydenstricker (351) We have seen cases where the vomiting, anorexia, labored breathing and inability to sleep contributed to severe pellagra

5 *Cardiazol therapy* de Langen (182) has mentioned this as a possible predisposing cause of pellagra in one instance We have never seen pellagra after insulin, metrazol or cardiazol therapy

6 *Sunstroke* Bickel (34) has recorded an instance of pellagra in an alcoholic where the diagnostic lesions appeared following sunstroke

7 *Allergy* Salama (299) has studied the relationship of pellagra to allergy but his conclusions scarcely support the idea of secondary pellagra except in the sense that some allergy diets used were poor in pellagra-preventive factors

8 *Therapy with thiamine* It has been reported that therapy with thiamine has been followed by an outbreak of pellagra (42, 236) In these cases, it is plausible that nicotinic acid deficiency would have become manifest regardless of other vitamin treatment It is possible that the use of one fraction of the vitamin B-complex puts a strain on the metabolism controlled by other factors and thus might bring out a latent deficiency This remains to be demonstrated in man

TABLE VIII

Miscellaneous

DISEASE OR CONDITION		CASES IN WHICH THE CONDITION WAS THE PRINCIPAL CAUSE			CASES IN WHICH IT WAS AN ACCESSORY CONTRIBUTING FACTOR	WHITE		COLORED		AVERAGE AGE
		Total	Ohio	Alabama		Female	Male	Female	Male	
Cirrhosis of the liver		17	15	2	3	5	7	3	2	49
Hemorrhage		8	4	4	8	4	—	4	—	39
Addison's disease		4	2	2	—	1	1	1	1	49
Diabetes		3	3	—	4	1	1	1	—	49
Hyperthyroidism		3	1	2	3	2	—	—	1	36
Myxedema		1	—	1	2	1	—	—	—	50
Carcinoma										
Lung	1									
Bladder	1									
Pancreas	1	7	4	3	3	3	3	1	—	51
Cervix	3									
Liver	1									
Bronchial asthma		6	—	6	2	1	4	—	1	55
Syphilis										
Aneurysm	2	4	3	1	12	—	2	1	1	57
Tabo-paresis	2									
Migraine		2	—	2	—	2	—	—	—	31
Hodgkin's disease		1	1	—	1	—	—	—	1	36
Morphine addiction		2	2	—	1	1	1	—	—	36
Paraldehyde addiction		1	1	—	—	—	1	—	—	34
Rapid growth		1	—	1	4	—	1	—	—	15
Totals		60	35	24	43	21	21	11	7	

9 *Acrodynia* Stephen (345) has suggested that the pink disease may be complicated by a secondary pellagra

10 *Leucemia* We have found no record of pellagra secondary to leucemia Our interest in such a possibility was stimulated by the finding in leucemia of instances of very low values for the blood codehydrogenases I and II by Viltei, Vilter and Spies (377) When one of the patients in this study later developed pellagra it added some evidence for the correctness of the speculations entertained concerning the relationship of these pyridine coenzymes to pellagra The following case is included for its interest rather than as evidence of the validity of our ideas concerning the pathogenesis of pellagra

Case report G H (W 96018), a 43-year-old housewife was admitted to the Cincinnati General Hospital December 27, 1939, for treatment of myelogenous leucemia She had noted an enlarged spleen a year before and the diagnosis of leucemia was made six months later when she was first studied on the medical service It was then found that her blood codehydrogenases were very low, ranging from 1-5% of that found in normal controls She had been given Roentgen therapy after a failure to reduce the leucocytes with colchicine The cells declined from 195,000 to 30,000 per cubic millimeter Radiotherapy over the spleen produced considerable local discomfort, nausea and vomiting An attempt was made to restore the blood codehydrogenases to normal by means of heroic doses of yeast and nicotinic acid with no significant increase She was discharged after six weeks and followed in the out-patient clinic with occasional treatment of the enlarged spleen with X-rays Before her last entry she had much trouble with vomiting and anorexia On the last admission physical findings of note were a spleen reaching down into the pelvis, liver firm and easily felt three fingers' breadth below the rib margin Petechial and purpuric areas developed in the skin There was extensive vaginal bleeding Blood study revealed 3 2 million erythrocytes and 82,500 leucocytes per cubic millimeter and 11 4 grams of hemoglobin per 100 cc On the 9th hospital day she was found to have a red tongue and the early skin changes characteristic of pellagra She was given large doses of various anti-pellagra compounds and many transfusions but died on the 16th day There was little improvement in her pellagra

Discussion The problems presented by this patient are very interesting from the point of view of pathogenesis of pellagra Her nutritional state was undermined by her chronic disease and particularly upset by the anorexia, nausea and vomiting Another possible contributory element was the series of X-ray treatments which may have acted in a specific fashion though pellagra was not encountered in any of the other patients with leucemia whose blood codehydrogenases were so low (377) Finally the increased metabolism (BMR + 20) and the loss of blood undoubtedly added their burden This case illustrates once more the difficulty of assigning a single specific cause to a given case of *secondary* pellagra where many different deleterious influences operate

XVIII THE INFLUENCE OF HEREDITY IN PELLAGRA

Although for two hundred years heredity has been considered a strong predisposing influence in pellagra there has never been a successful demonstration of this belief Muncey (239) and Davenport (79) after extensive studies concluded heredity was a factor in determining the type of symptom complex which occurred but it was not inherited in the same way as eye color H F Harris (150) and other exponents of the maize theory have had to rely on hereditary influences to explain pellagra where no corn had been eaten by the victim This led Harris to the *reductio ad absurdum* that all cases of pellagra were inherited, symptoms appearing only when the patient plus his ancestors had eaten enough corn Pellagra occurs in families Children born of pellagrous mothers are apt to have pellagra Large families are more liable to have several pellagrins than small ones in the same economic circumstances The chemical phase of nicotinic acid deficiency may occur in utero, paving the way for pellagra in the infant We have seen pellagra in an infant 3 weeks old who was 2 months premature In this manner pellagra may be congenital but not inherited Pellagra in the father does not have this tendency We have not seen adequately fed children of

pellagrous parents develop pellagra It is interesting that the onset of pellagra has not been reported in artificially fed infants but usually occurs only if the mother has been deficient in providing for the child in utero and during lactation An analogous situation is true in riboflavin deficiency (337) and has been known in beriberi for a long time (372)

Even though almost all arguments favoring a potent hereditary predisposition in pellagra can be explained on the accumulated information available on dietary factors, a rôle for inherited liability to the disease has by no means been ruled out of court Cowgill (71), Brown (48) and Light and Cracas (191) have shown that even carefully chosen experimental animals have wide individual variations in susceptibility to different dietary deficiencies Litter mates vary and extreme differences occur in different strains MacCarthy (199), Mainzer (212) and Otonello (257) have reported some interesting examples favoring hereditary predisposition in human beings

A study of secondary pellagra throws light on the occurrence of this condition in several generations We have found that a positive family history (parent, grandparent or sibling) was obtained from 81% of all pellagrins in the endemic area [3] This is in sharp contrast to the 1 3% in the Ohio group with secondary pellagra It is possible that this reflects a true hereditary hypersusceptibility to pellagra in the endemic region More probably it indicates merely an identity of environment, food habits, and economic level—a situation into which the pellagrins are thrust, rather than a handicap brought along with the germ plasm

It has been remarked that the dissimilar incidence of whites and negroes in an otherwise homogeneous group of pellagrins is strong indication of a racial predisposition in the whites and relative immunity in the colored (79, 200, 239) In the Birmingham group negroes constituted only 9% of all patients [4] This has been reported before in the southern states (351) Almost all had secondary pellagra In the Ohio group negroes were between two and three times as numerous as one would expect on the basis of their ratio in general population or hospital admissions In other words pellagra as we have encountered it in the negro seems to occur chiefly as a sequel to organic disease We believe food habits and perhaps energy conservation are much more important reasons for the rarity of endemic pellagra among negroes than hypothetical racial exemption Final proof is not yet at hand Pellagra is rare among Hebrews in our experience, but cases do occur

XIX CONCLUSION

The general background of secondary pellagra has been considered in detail and a comparison has been made between the natural history of disease complicated by pellagra in the endemic area in Alabama and in two Ohio hospitals While the two groups are not homogeneous samples of the populations in their

[3] This is artificially increased because we attempt to study the entire family of any pellagrin who visits the Birmingham Nutrition Clinic and in some instances as many as 10 in a single family have been found to have pellagra at the same time

[4] Negroes constitute slightly more than a third of the total population of Alabama

respective areas and our data do not warrant statistical analysis, certain contrasting patterns of disease reflect strong local influences (27) The pattern of infections reveals the damaging influence of pulmonary disease in Ohio and of malaria in Alabama Pregnancy and lactation seem to be very influential in determining the eruption of pellagra in regions of endemic malnutrition More than any other factor, childbearing and its inherent complications predispose the susceptible segment of the population to pellagra where diet is near the borderline of inadequacy The rôle of surgical operations has been considered at length, and the many ways in which operations and untoward sequels thereto may dispose to or even precipitate pellagra have been discussed In this study we have tried to show that disease and accident of multiplex variety are conditioning influences of extreme importance in nutrition It is only natural that this miscellany of illness and misfortune be a more perilous burden in persons whose nutrition has been such that no margin of safety exists to meet a crisis For that reason pellagra often resulted when trivial sickness occurred in the ill-nourished folk studied in Alabama whereas in the Ohio municipal hospitals pellagra followed more severe and disabling disease In the endemic territory pellagra may be chronic, recurring with the seasons, worse when other disease is present, sometimes escaped during periods when the general health is good In Ohio, pellagra frequently dominates the terminal stage in cancer, cirrhosis or heart failure

Secondary pellagra thus reflects the mosaic of the prevalent diseases upon which it is engrafted Among peptic ulcer victims or those suffering from cancer of the stomach more males than females are affected In pellagra following measles children naturally predominate This is in notable contrast to the disease as it appears where the chief and sometimes only cause is dietary In endemic pellagra older children and the young men are less frequently affected while the bulk of pellagrins is found among the women from 20 to 40 years old, the younger children and the older men

It is our belief that the many diseases which may form the background for pellagra operate in a simple manner in working this mischief A great deal more effort must be forthcoming to bring evidence which will establish or clearly disprove current notions concerning the pathogenesis For that reason we have emphasized the facts collected, the diseases and classes of disorders which pellagra may complicate, rather than the hypothesis which we have used to integrate the picture But any study which is not directed by haphazard empiricism must have some underlying idea We have, therefore, assumed about pellagra much that we do not know for a certainty Our interpretations are congruent with our observations This conception of pellagra may be stated in brief

Pellagra appears to be the result of an inadequate supply to the human body of certain preformed constituents of food which must be available in small but definite quantities The need for these materials (nicotinic acid amide, phosphorous, protein and perhaps other things) is proportional to the metabolic requirements for a given period While storage and other mechanisms of homeostasis allow some margin of safety a reasonably constant intake of these sub-

stances is essential for health The most frequent cause of an upset in this nutritional balance is a failure of the supply This blockade may result from a poor diet or from any functional or mechanical obstacle to ingress anywhere along the alimentary canal Similarly an increased loss by vomiting, diarrhea, fistulae or by diuresis or even sweating may carry off enough of the required essences to result in dangerous deficiencies From the other side an elevated demand may result in a discrepancy between need and the satisfying of it which leads to results just as disastrous Fevers, neoplasms, parasites and childbearing may thus overthrow the balance by enhancing requirements in the face of a constant supply Often many influences are at work in a single case It is quite apparent that deficiencies must exist in a humoral stage first Then functional disturbances occur when the biochemical lesion interferes with cellular function though leaving no tell-tale sign for the clinician Finally these changes become translated into morphological lesions which we recognize as the hallmark of a deficiency disease or syndrome This points the lesson that what we see and recognize as pellagra, the visible part of the iceberg, presages a widespread subsurface danger, that malnutrition of a serious nature is more prevalent than this survey of secondary pellagra indicates

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ACRIDINE ANTISEPTICS

A Review

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The sulfonamides representing the nearest approach to the ideal in synthetic chemotherapeutic agents are often found to be ineffective Penicillin and other antibiotics offer but a limited solution to the problem due to supply and cost of production The development of bacteria which are resistant to the action of both types of agent suggest the need for an expanded armamentarium in the fight against disease Acridines and diamidines have recently been employed by British Medical Units operating on the African front The report of Mitchell and Buttle (69) has been primarily responsible for a revival of interest in the acridine compounds

In the course of preparation of this review, it became apparent that the literature of the period preceding the year 1932 need not be covered in detail for two reasons First, there are two comprehensive reviews of this literature (89, 14) Second, much of the work of that period was complicated by a failure on the part of the investigators to realize that they were dealing with impure compounds This was particularly true of the studies of acriflavine, since with this compound it seems reasonably certain that no two batches were the same It is desired here to review only as much of the older literature as is necessary to an understanding of the more recent literature on the subject

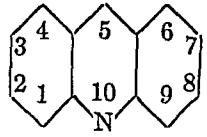
Acridine derivatives and, it is hoped, many other series of compounds may supplement or augment the application of chemotherapy in those cases in which bacteria are fast to sulfonamides and to anti-biotics It is to be expected that fastness or resistance of bacteria will become a widespread and commonly occurring phenomenon The only answer to this challenge lies in expanding effort to broaden the scope of chemotherapy

CHEMISTRY

Bender in 1889 (14) prepared the first of the acridine compounds, acridine yellow, acridine orange and others Some years later in 1912, Benda (4) prepared diaminoacridinium methylchloride, and Ehrlich found it to be trypanocidal During the first World War, Browning (1, 3, 55) in England and Shiga (90) in Germany conducted extensive investigations of the value of the acridines as wound disinfectants The following table lists all of the acridine com-

TABLE 1

Acridine derivatives in chemotherapy



COMPOUND	REFERENCE	CHEMO EFFICACY	L D 50	PARTS PER 100,000 PRODUCING 50% DEPRESSION OF FROG'S AURICLE (76)	SUBSTITUENTS IN POSITION									
					1	2	3	4	5	6	7	8	9	10
Acriflavine	1, 2, 3, 4	++++	0 05 g /kg (1)	100		NH_2						NH_2		CH_3 Cl
Proflavine	See 2 8-diaminoacridine					NH_2						NH_2		
Iodoflavine	5	++	15 mg /kg (1)			NH_2						NH_2		CH_3 I
1-aminoacridine	9,12	–			NH_2									
2 aminoacridine	9,12	++++	0 35 g /kg (o)	30		NH_2								
3-aminoacridine	9,12	+					NH_2							
4-aminoacridine	9,12	+	0 3 g /kg (o)	30				NH_2						
5 aminoacridine	9,12	++++							NH_2					
3-7-diaminoacridine	8						NH_2				NH_2			
3 6-diaminoacridine	9		0 7 g /kg (o)	500			NH_2			NH_2				
1-3-diaminoacridine	8,9		0 2 g /kg (o)	20	NH_2		NH_2							
1-7-diaminoacridine	8,9		0 5 g /kg (o)	3	NH_2						NH_2			
2 5-diaminoacridine	8,9	++++	0 3 g /kg (o)	>100		NH_2			NH_2					
2-6-diaminoacridine	8,9	++++	0 35 g /kg (o)	>100		NH_2				NH_2				
2-7-diaminoacridine	8,9	++++	0 5 g /kg (o)	>100		NH_2					NH_2			
2-8 diaminoacridine	8,9	++++	0 2 g /kg (o)	>100		NH_2						NH_2		

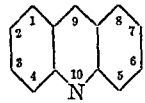
2 9-diaminoacridine	8 9	–	0 75 g /kg (o)	10		NH_2							NH_2	
2 8-diaminoacridone	9	–	0 5 g /kg (o)											
2-amino-8-acetamido-acridine	9	++	0 38 g /kg (o)	30		NH_2						N^{H}_{Ac}		
Acridine orange	14					$N^{CH_3}_{CH_3}$						$N(CH_3)_2$		
Acridine yellow	1	++				NH_2	CH_3				CH_3	NH_2		
Benzoflavine	14					NH_2	CH_3				CH_3	NH_2		
Brilliant acridine orange	14					$N^{CH_3}_{CH_3}$						$N^{CH_3}_{CH_3}$		
Chrysaniline	14					NH_2			NH_2					
Brilliant phosphine nitrate	14					NH_2	CH_3				CH_3	NH_2		CH_3 NO_2
Flavacid (Langer s acridine)	6	+++++	300 mg /kg (o)			$N^{CH_3}_{CH_3}$	CH_3				CH_3	NH_2		CH_3 Cl
Brilliant phosphine imino	6	++	5 mg /kg (i)			$N^{H}_{CH_3}$	CH_3				CH_3	$N^{H}_{CH_3}$		CH_3 NO_2
di m aminobenzoyl rivanol	14						OC_2H_5		NHR			NHR		
Phenylacridine	82	++												
3 7-dioxy 2 8-dimethyl acridine	82	–				CH_3	OH				OH	CH_3		
Sinflavine	5	++++	15 mg /kg (i)			OCH_3						OCH_3		CH_3 Cl
Rivanol	7	+++	50 mg /kg (i)	3			C_2H_5O		NH_2			NH_2		

TABLE 1—*Continued*

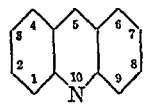
COMPOUND	REFERENCE	CHEMO EFFICACY	L D 50	PARTS PER 100,000 PRODUCING 50% DEPRESSION OF FROG'S AURICLE (76)	SUBSTITUENTS IN POSITION									
					1	2	3	4	5	6	7	8	9	10
3-ethoxy-5-aminoacridine	7	++					C_2H_5O		NH_2					
5-aminosinflavine	5	++++	10 mg /kg (i)			OCH_3			NH_2			OCH_3		
Methochloro-5-aminosinflavine	5	+				OCH_3			NH_2			OCH_3		CH_3 Cl
Stuckey compounds	8,11						C_2H_5O		Cl		CH_3O			
Stuckey compounds	8,11						C_2H_5O		Cl			CH_3O		
Stuckey compounds	8,11						C_2H_5O		Cl				CH_3O	
Morgenroth compounds	7					OC_2H_5			NHC_2H_4OH					
Morgenroth compounds	7						RO		NHC_2H_4OH					
Chloroaminoacridines	8,9	++++	0 13 g /kg (o)	0 03		Cl			NH_2					
Chloroaminoacridines	8,9					NH_2				Cl				
Chloroaminoacridines	8,9					NH_2					Cl			
Chloroaminoacridines	8,9					NH_2						Cl		
Chloroaminoacridines	8,9					NH_2							Cl	
Chloroaminoacridines	8,10						NH_2			Cl				
Chloroaminoacridines	8,10						NH_2				Cl			
Chloroaminoacridines	8,10						NH_2					Cl		
Chloroaminoacridines	8,10						NH_2						Cl	
Mepacrine	14					Cl			NHR		CH_3O			
Nitroaminoacridine	13								NH_2			NO_2		
Nitroaminoacridine	13								NHR			NO_2		
Nitroaminoacridine	13						RO		NHR			NO_2		
Acridine	9	−	0 3 g /kg (o)											

(i) = intraperitoneal, (o) = oral

pounds found in the literature They are based upon the acridine unit which was numbered



in the German literature but is considered in this review and in the English literature as based on the following position number system



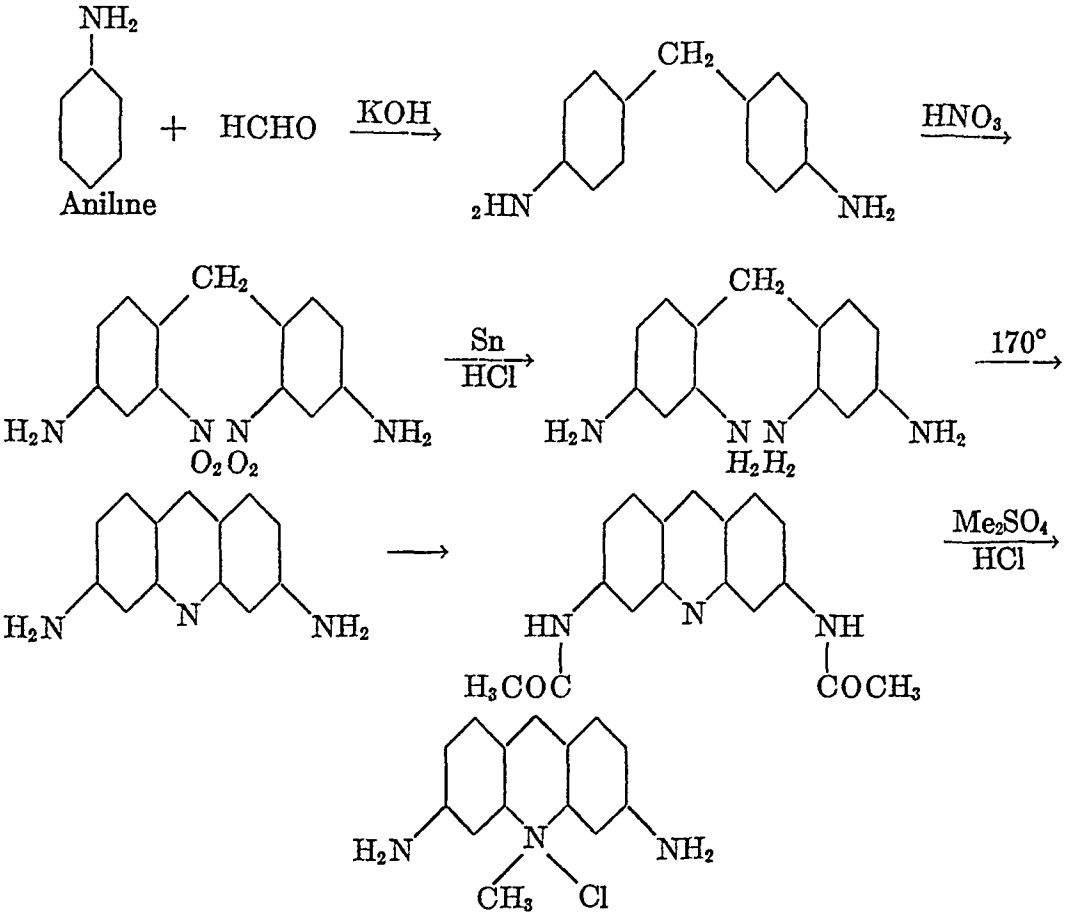
Thus in the German system, trypaflavine would be 3 6 diaminoacridinium methyl chloride, while in the English system used here, it is chemically named 2 8 diaminoacridinium methyl chloride

It was decided to use the English nomenclature system as Albert and his group (2, 9, 20, 21, 22, 100, 101) have made outstanding contributions to the chemistry and general knowledge of these chemotherapeutic agents using the English system throughout their work It is to be emphasized that great confusion exists because of this variation in the numbering system Some English books on chemotherapy, i e May and Dyson (91) use the German system

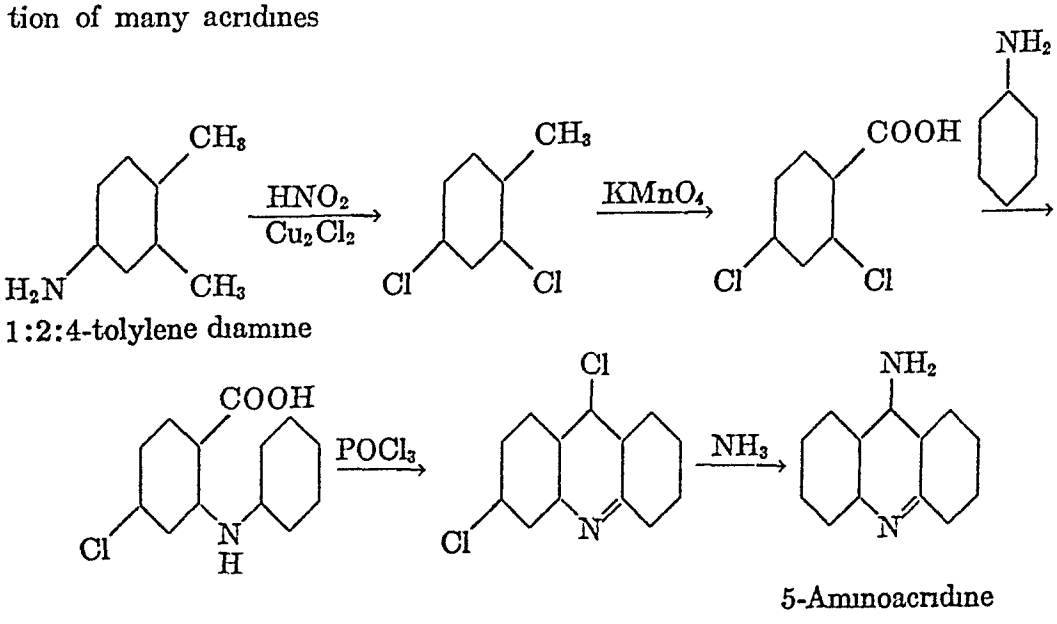
Chemically the acridines are related to the quinolines The parent substance of this group of compounds is acridine, which is contained in small amounts in coal tar It is obtained synthetically by heating diphenylamine with formic acid and zinc chloride Many of the derivatives under consideration are excellent dyes Acridine orange, for example, is used commercially as the zinc chloride double salt It gives a fluorescent color on cotton and silk which is fast to washing and to light

The number of these agents makes it impossible to discuss their preparation in any detail Therefore, two typical members are considered proflavine and acriflavine The procedure of Benda (4) was to react aniline with formaldehyde and potassium hydroxide using heat and addition of aniline hydrochloride Diaminodiphenylmethane was formed and nitrated The nitration product was then reduced with tin and hydrochloric acid The reduction product which contains the tin double salt of tetraaminodiphenylmethane was heated in an autoclave at 175° to form 2 8 diaminoacridine, or proflavine Proflavine is converted to acriflavine by acetylating to protect the amino groups and then methylating with methyl sulfate or methyl toluenesulfonate in nitrobenzene solution The acetyl groups are then hydrolyzed from the resulting compound

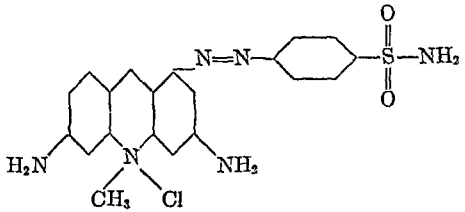
by heating with hydrochloric acid, and on cooling the desired hydrochloride crystallized out in red needles. The reactions are



The method of Albert, et al (9) for the synthesis of 5-aminoacridine illustrates another synthetic procedure adaptable with modification to the production of many acridines



The ease with which acridine will form azo compounds has led to the synthesis of sulfonamido-azo-acridinium complexes (92) which might prove of value in chemotherapy The general structure of these compounds is illustrated by the complex formed between sulfanilamide and acriflavine

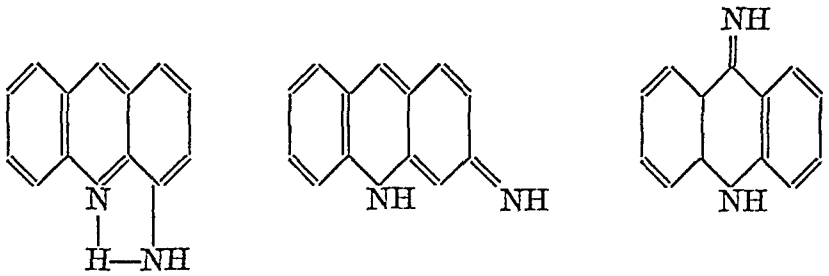


Gailliot (15) stated that acriflavine as described in the British Pharmacopoeia was not the hydrochloride of 2 8-diamino-10 methyl acridinium chloride but consisted of a mixture of equal parts of this compound with diaminoacridine hydrochloride Proof was based upon the methyl content of the acriflavine BP and on solubilities His method of separation was to add a suspension of silver oxide, made from 20 grams of silver nitrate, to a solution containing 20 grams of the crude methyl chloride in question, dissolved in 1,500 ml of water The insoluble matter was filtered off on a vacuum filter and was mainly the diaminoacridine The filtrate contained the methylacridinium hydrate which on the addition of potassium iodide formed a voluminous precipitate of acriflavine iodide Gailliot (15) presents detailed studies of the solubilities of the pure compounds and of mixtures of the pure compounds

Hall and Powell (16) found that the NNR directions for the detection of pure acriflavine were of little value The test supposedly depended upon the interaction of diaminoacridine and formaldehyde to form a precipitate Acriflavine does not react These workers point out that the reaction is of no value since it depends upon the presence of sulfate, and when sulfuric is present both acriflavine and diaminoacridine give precipitates The formaldehyde nitrite test is regarded by these investigators as having value It depends upon the reaction of proflavine with sodium nitrite in the presence of formaldehyde A violet color is produced which on further addition of sodium nitrite results in the formation of a brownish violet precipitate After a few minutes, the solution becomes colorless This test is of value in distinguishing acriflavine from proflavine and also in detecting acriflavine in diaminoacridine dihydrochloride but is of no value in detecting the latter in acriflavine Marshall (17) confirmed these observations and stated that from commercial samples of acriflavine only about 12% pure acriflavine could be recovered He also reports that alkali very quickly converts acriflavine into diaminomethylacridone In 1941 Berry (18) found that acriflavine and proflavine and mixtures of the two in varying proportions do not differ in their bacteriostatic value It is his conclusion that mixtures containing about 30% of diaminoacridine are slightly more soluble than each component or other mixtures

Proflavine, which has become the acridine of choice, is an orange red, odorless, crystalline powder, dissolving in water and alcohol to give reddish solutions which have a green fluorescence on dilution One part is soluble in approximately 300 parts of water It is stated that, "A 0 1% solution has a pH of 2 5 to 2 7, while a 1 in 1,000 solution can be buffered to pH 6 3 without precipitating the base" (19) Proflavine sulfate may be boiled or heated in an autoclave to 130° without decomposition The chemical is sensitive to light

In a series of articles (20, 21, 22, 12) a direct correlation between basicity and antiseptic action has been clearly demonstrated In the first of the series, Albert et al (21) found a direct correlation between basicity and antiseptic action Considering the monoaminoacridines, they suggested that the inactivity of the 1-aminoacridine was due to hydrogen bonding, whereas, with the 2 and the 5-monoaminoacridine the activity was due to the formation of acridonimines This is illustrated by the formula

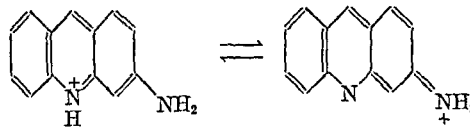


1-Aminoacridine 2-Aminoacridine 5-Aminoacridine

In the second paper of the series (20) it was shown that the most active of the monoaminoacridines are the most basic and the most hydrophilic, whereas the least basic and most hydrophobic members have only feeble antiseptic action It is in this paper that these workers first recommend 5-aminoacridine because of its non-staining qualities Actually, there are other non-staining members of this group These non-staining acridines possess certain advantages over the others The most promising is 5-aminoacridine (12) Hata (5) described two such non-staining chemicals, namely, sinflavine, 2,8-dimethoxyacridinium methylchloride and 5-amino-2,8-dimethoxyacridine chloride Both proved effective in vitro and in vivo

In 1942, Albert et al (12) concluded that there were three general classes of monoaminoacridines Class 1, with marked antiseptic action associated with relatively high chemical basicity and the imino grouping, Class 2, with moderate antiseptic action, moderate basicity and possessing the normal amino grouping, and Class 3 with little or no antiseptic action and possessing an abnormally low basicity associated with an amino group that is masked through hydrogen bonding Proflavine, and 2 and 5-aminoacridines are assigned to class 1, 3- and 4-aminoacridines to class 2, and, 1-aminoacridine to class 3 The interpretation advanced that the more active drugs owe their increased antiseptic action to the presence of the peculiar imino structure is interesting viewed in the light of recent work on the sulfonamides which demonstrated that resonance is

the deciding factor in potency With the acridines, these forms (the imino forms) would not be important if they did not lead to resonance between the ionic forms, e g in the case of 2-aminoacridine



Bell and Roblin (95) have demonstrated that in the case of the sulfonamide it is the acidic dissociation and the negative character of the $—SO_2$ group which determine activity The more negative the $—SO_2$ group of an N_1 substituted sulfanilamide derivative, the greater is its bacteriostatic power With the sulfonamides acidity is not the sole determining influence, as in the heterocyclic series the bacteriostatic activity increases to a maximum and then falls off with increasing acidity With the acridines it is not basicity alone, as some of the more strongly basic compounds are not good antiseptics In the sulfonamide series, it is the electronegativity of the SO_2 group, and in the acridine series it would seem to be the electropositivity of the ring or amino nitrogen radical

BIOCHEMISTRY

Fuehner (23) found that acridine was partly oxidized to hydroxyacridine and excreted in conjugation with sulfuric acid and glucuronic acid Trypaflavine and proflavine disappear rapidly from the circulation (24) Following intravenous injection of the nitrate, only one-thirtieth of the injected material could be detected after 20 minutes, and with the sulfate even less after 10 minutes These acridine derivatives (25) are excreted largely by way of the liver and the kidney in bile and in urine

The rate of bacterial adaptation is a factor affecting the treatment of infections with antiseptics It is biochemical in nature and will, therefore, be considered in this section Burke et al (26) found that Staph albus developed resistance to acridines within six to eight hours of exposure The adaptation to the dye was temporary and disappeared when the organism was grown on dye-free agar Staph albus could be separated into two strains which differed in their ability to tolerate neutral acriflavine Where originally a concentration of 1 in 1,000,000 inhibited growth, after adaptation the bacteria would grow in concentrations of 1 in 1,500 The work of McIlwain (27) has disclosed the nature of the mechanism of adaptation in these bacteria Using Bacterium coli and Strep hemolyticus, he found two types of material which were needed for growth in the presence of the acridines but were not needed in the normal bacteria Type 1 was nucleotides, and type 2 was a concentrate of amino acids for which phenylalanine could be partially substituted Type 1 compounds formed complex salts with acriflavine components, and McIlwain considered that the inhibitors inactivate enzyme systems of which type 1 compounds are an essential part, and type 2 compounds are substrates or products, some of which can be replaced by hydrogen carriers

Quastel and Wheatley (28) in studying the action of dyestuffs on oxidation found that basic dyestuffs, one of which was acriflavine, were highly toxic, and yet Quastel (29) found that even at concentration of 1 in 2,000, fumarase from brain was not inhibited above 12% There was 100% inhibition of fumarase by such agents as congo red, trypan blue, acid green, methyl violet, benzopurpurin, etc Selecting another universally occurring enzyme, urease, Quastel (93) extended her work on the action of dyestuffs on enzymes Acriflavine at 1 in 2,000 concentration inhibited purified urease by some 72%, even at 1 in 10,000 the inhibition amounted to 3% This was a general property of all basic dyes and could be prevented by various amino acids and diamines

Inhibition of the Pasteur reaction by acridine dyes has been reported by Dickens (30) He suggests that the general similarity to the Warburg pyridine body, the active group of the hydrogen transporting and fermentation enzymes, is sufficiently marked to warrant the conclusion that the action is by displacing the coenzyme through preferential adsorption on the colloidal carrier, forming an inactive complex It is the opinion of the author that this is the first expression of the principle of selective adsorption of metabolic analogues Dickens points out that the quaternary nitrogen is not the key, as phenazine methiodide exerts a powerfully catalytic action in the Pasteur system instead of acting as an inhibitor Manifold (31) examined acriflavine, proflavine, 2 7-diaminoacridine hydrochloride and other antiseptics for their action on glucose and pyruvate oxidation systems of brain tissues Acriflavine was extremely toxic even at very low concentrations Proflavine sulfate was much less toxic than acriflavine and 2 7-diaminoacridine was significantly less toxic than proflavine sulfate Manifold could not reverse the enzymes systems inhibited by the acridine antiseptics

CHEMOTHERAPY

The consensus of opinion of workers in the field of the acridines would seem to be that due largely to their toxicity, they are of little value for general systemic application Again, no attempt is made to review in detail the rather extensive literature on this aspect of the acridines, which is covered in other reviews (14, 89) The present author is of the opinion that unmodified acridines, excepting 5-aminoacridine and 2 7-diaminoacridine, are of little value in systemic therapeutics Since it is possible that the crude drugs used in the past were responsible for many of the accidents which occurred, further trial is indicated The toxicological results will be treated in the next section

Ehrlich, using acriflavine (trypaflavine) prepared by Benda (4), first demonstrated the chemotherapeutic effect of these chemicals in trypanosomiasis To Browning and his school in England goes much of the credit for the early application of the acridine series in the fight against bacterial disease From a consideration of the literature it becomes immediately obvious that a profound controversy existed and still exists, a controversy which can be settled only by further clinical research

The surprising potency of acriflavine against gonococcus (32, 33), active 1 in

50,000,000, led to its use in the clinical management of gonorrhea Davis (34) gave 0 1 grams of acriflavine by mouth and found it was secreted in the urine in concentrations great enough to render the urine unfit as a culture medium for colon bacillus and staphylococci, provided the reaction of the urine is alkaline After this dosage the antiseptic persisted for eight hours In his practice, acute urinary infections responded immediately Chronic urinary infections did not respond readily Improvement was noted in 60 per cent of the cases In acute anterior gonorrheal urethritis, acriflavine is not a dependable prophylactic for preventing extension to the posterior urethra 30% of his patients showed a mild catharsis and some nausea In 5% there was vomiting and diarrhea In 1932 Davis (35) again reported on urinary antiseptics and stated that acriflavine in alkaline urine is an unfailing antiseptic Some support of this work was presented by Hughes and Birch (36) They found that if acriflavine is given by deep subcutaneous injection, it will cause urethral discharge to disappear quickly, but that relapses are common and that local pain at the site of injection makes it unsuitable for use in an out-patient clinic Jaundice was noted following acriflavine A tendency to lessen the incidence of complications in gonorrhea was the final tribute of these workers to acriflavine

The most recent clinic report on the use of acriflavine in the treatment of gonorrhea is that of Assinder (37) who found that in 4,985 cases of acute disease treated with acriflavine the duration of urethral discharge was markedly reduced As a rule, the discharge disappeared in 7 to 10 days, which was much less than was usual in his cases treated with irrigation alone If the posterior urethra is affected, acriflavine (which is being continuously excreted into the bladder) helps clear up the cystitis, while if the posterior urethra is not affected, the acriflavine apparently protects it Results in coli cases compared favorably with mandelic acid Assinder states that liver damage as observed by others is entirely due to the use of impure acriflavine He had been getting some bad results and completely eradicated them by using purified acriflavine It would seem possible that acridine antiseptics might prove of value in sulfonamide resistant cases of gonorrhea

There have been many reports of the successful treatment of meningococcic meningitis (38, 39, 40, 41, 42) with acriflavine Recently, Puig (42) reported cure of meningitis following the use of proflavine Wegeforth and Errick (43) demonstrated in rabbits the effectiveness of the flavines in the treatment of meningitis, experimentally produced They noted, however, that even small amounts of the flavines produced pathological changes in the meninges

The possible value of the acridines as intestinal antiseptics has been investigated by Graham (44) The mice used in the study received proflavine by stomach tube In no instance, however, was there significant diminution in B coli or other members of the usual aerobic flora of the bowel Acriflavine, according to Graham, was effective against intestinal infections with Schistosoma intercalatum It is the opinion of the present author that this work does not eliminate the potentialities of the use of acridines as intestinal antiseptics By comparison, sulfanilamide did not prove very efficient as an intestinal antiseptic

Other sulfonamides have Rivanol is ineffective as an intestinal antiseptic (45) but is an effective agent in the treatment of amoebic dysentery (46)

Acriflavine has been reported (14) effective against trypanosomiasis in animals and against sleeping sickness in human beings, ineffective against malaria in human beings or birds, effective in piroplasmosis in dogs, effective against staphylococci, coli and streptococci, ineffective against pyocyaneus, tetanus and gas bacillus, effective against wound diphtheria, effective against pneumonia in mice, effective against chicken cholera, anthrax and cholera, inactive against mouse arthritis, inactive against typhus, inactive against tuberculosis

It seems that most investigators believe that acridines are more effective against staphylococci than against streptococci Rivanol is effective against staphylococci, streptococci, gonococci and amoebic dysentery The acridines seem to be generally ineffective against proteus and pyocyaneus probably due to nutritional requirements which permit these bacteria to synthesize the factors specifically displaced by acridines

The controversy revolving around the use of acridines in the treatment of superficial wounds is due largely to the discussion of whether or not flavines are bactericidal in concentrations at which they do not injure leucocytes or fibroblasts It would seem that the evidence favors the view that they are valuable drugs for use in local chemotherapy

German (50) found the highest efficiency of acriflavine at concentration of 1 in 1,600 Acriflavine exerted an inhibiting effect on fibroblasts, while not particularly altering epithelial proliferation From his studies, German concluded that acriflavine was one of the few antiseptics exerting bactericidal effect in dilutions compatible with tissue viability Mueller (51) reported that all of the acridines were less effective when tested in broth or in broth plus serum Agglutination of human red corpuscles by flavine and acriflavine in dilutions up to 1 in 3,200 was noted by Fleming (52) A strong anticoagulant effect on human blood in concentrations of 1 in 2,000 was found The dyes completely inhibited leucocytic emigration, and had a destructive action on the leucocytes Thus, with acriflavine Fleming felt that the leucocidal action greatly exceeded the bactericidal action In blood serum a concentration of 1 in 32,000 permitted growth of staphylococci, B coli grew in 1 in 1,000, and B proteus grew in 1 in 2,000 concentration When acriflavine was injected in large doses, the flavine immediately disappeared from the blood which acquired no bactericidal power The flavine was taken up by the tissues which became yellow but acquired no inhibitory power for the growth of bacteria Drummond and McNee (53) reported absence of toxicity but little else favoring the use of acriflavine They state that acriflavine cannot be classed as a success in the treatment of later stages of war wounds It was their opinion that processes of repair were completely inhibited Colledge et al (54) could find no advantage in the use of proflavine over acriflavine The effect of hydrogen ion concentration on the effectiveness of the acridines was emphasized for the first time by Browning, et al (55) They noted that the antiseptic action of acriflavine and proflavine was greater in slightly alkaline solution The most favorable alkalinity was equivalent to

0 001 N sodium hydroxide The results obtained seemed much better when the pH was adjusted by the use of phosphates Browning had previously stated (1) that acriflavine was the most powerful bactericidal substance for both staphylococcus and B coli, and it was equally efficient for the enterococcus and for anaerobes such as B oedematis maligni Browning's second paper (2) with the same coworkers stated that acriflavine exerts a slowly progressive bactericidal action Concentrations of this substance which at first inhibit and then kill bacteria are without harmful effect on phagocytosis Bond (56) devised an ingenious method for testing leucocyte activity which he applied (57) to the acridine antiseptic then used, namely, acriflavine His conclusions were that there was no evidence of toxicity of acriflavine for leucocytes in the concentration recommended Three preparations were used acriflavine soap paste made from neutralized stearic acid and sodium carbonate with 0 1% acriflavine, an acriflavine gelatin made by incorporating 0 1% acriflavine, and, finally, an acriflavine starch preparation Bashford et al (58) report that in their experience treatment with flavine (1 in 1,000) results in small formation of pus, slow epithelial ingrowth, delay in all processes of repair, lingering of organisms in the wound surface, and some diminution in the local and general reaction to infection Results were essentially the same with proflavine or acriflavine This report of the Bashford group is a clear cut condemnation of the use of the flavines

Recommendation of acriflavine in the treatment of streptococcus infected wounds was made by Schiemann and Wreschner (59) Browning and his coworkers (60) again came to the defense of the flavines in an article in which they reported results on 600 burn and pyogenic infection cases treated with acriflavine or proflavine Clinically there was no interference with formation of granulation tissue, no evidence of pellicle formation or necrosis, and no tendency to hemorrhage Ossification proceeded actively in periosteal granulation tissue under application of flavine Epithelial regeneration, in the form of ingrowth from surrounding skin and grafts, proceeded actively in contact with dressings soaked in flavine solution Histological examinations in representative, unselected cases have confirmed and supplemented the clinical observations Browning had used a 1 in 1000 concentration applied on sterile gauze in burns, ulcers of the leg, carbuncles, cellulitis, osteomyelitis, acute suppurative bursitis, abscesses, septic hands, and fistula in ano In this article Browning and his coworkers completely refute the claims of Bashford et al (58), Drummond and McNee (53), etc Eggerth in 1926 (61) took a stand somewhat in between He concluded that the acriflavines might be useful in infections that did not tend to become rapidly generalized His observations on the bacteriological aspects of flavine usage were illuminating

The germicidal titer of acriflavine was markedly influenced by the nature of the medium in which the tests were made Meat infusion [illegible], lowered the titer The action was very different at varying hydrogen ion concentration alkaline reaction increasing the germicidal action Certain [illegible] had an adjuvant action on the acriflavine titer, differing according to the [illegible] used Metabolic products of streptococcus inhibited the action of the flavines Pus

greatly reduced activity Burke et al (26) recommended alteration of acriflavine and gentian violet in wounds This recommendation was based on the ease with which bacteria acquire resistance to any given chemotherapeutic agent The concept of alteration of chemotherapeutic agents seems sound in view of recently recorded results on the use of flavine following sulfonamides Hawking (87) found proflavine most effective in preventing infection in wounds, but he used solutions of the acridines and feels (94) that the application of powders of proflavine or of 5-aminoacridine to fresh non-suppurating wounds is contraindicated This conclusion is based upon his work in which he placed these chemicals as powders under the skin of rats and found extensive necrosis in every case McIntosh and Selbie (104) using a new and more reliable technique for testing chemotherapeutic agents report that acridines possess a fairly powerful action against all three anaerobes tested, Cl welchii, Cl oedematiens and Cl septicum No single agent was effective against all three agents, and these investigators recommend a combination of proflavine and sulfathiazole, 1 to 100, in an oil in water base

Garrod and Keynes (62) called attention to the disadvantage of the acridines manifested in their being adsorbed on the material of the dressing so that little gets to the wounds unless an excess of the acridine is present Further, their experience disclosed that the activity of acridines is inhibited by preparation with an oily base 0 2% solution of acriflavine is recommended The relative ineffectiveness of the acridine against B proteus and B pyocyaneus is emphasized At 1 in 100,000 acriflavine is effective against streptococci and staphylococci

Fleming (63) in 1938 again attacked the acridines by stating that in a 24 hour period, 1 in 2,000,000 acriflavine solutions destroyed leucocytes, while at this concentration acriflavine had no antiseptic activity whatever He emphasized the importance of the time element in evaluating the comparative studies with leucocyte destruction and bacterial inhibition In five hours, the phagocytic activity of leucocytes was seriously impaired by a dilution of 1 in 500,000 of acriflavine In a symposium held in 1940 in England, Fleming (64) again emphasized his results showing that leucocytic function is damaged in dilutions which are not bactericidal Garrod (65) at the same conference disagreed with Fleming (64) and suggested that failure to check the purity of the flavine preparation was responsible for the variation in results He reported that 1 in 2,000 concentration of acriflavine reduced leucocytic activity but did not abolish it

This section of the review has been presented chronologically as it is the belief of the author that Garrod (65) is fundamentally correct in his statement that purity of the chemical was the factor in many of the results reflecting on the usefulness of the acridines It was not until 1940 that this fact was considered by clinicians although Gailliot (15) had reported it in 1934 Berry (18) also emphasized the purity factor and recommended substitution of proflavine for acriflavine The present author feels that physiological and biological experimentation involving flavines should be accompanied by chemical data as to purity Personal experience has taught the extreme difficulty of obtaining flavines in a

chemically pure form, and it is almost certain that relatively impure preparations have been used in much of the work presented in the past few years

Jacoby et al (66) report that proflavine exerts a total and irreversible inhibitory effect, accompanied by disintegration of cells at concentrations lower than 1 in 1,000,000 Work was done on fibroblasts Acriflavine at 1 in 1,000,000 in 30% serum caused complete disintegration of macrophages in 24 hours Inhibition of epithelia from the gut of a 10 day old chick occurred at concentrations between 1 in 100,000 and in 1 in 120,000 In 1941, Russell and Falconer (67) tested acriflavine, euflavine, proflavine sulfate and 2 7-diaminoacridine on cerebral tissues Of these the first two inflicted uniformly disastrous effects upon the brain, hemorrhage and necrosis were conspicuous features These investigators recommend 0 1% isotonic solution of proflavine sulfate buffered to pH 6 2 as the antiseptic for prophylactic treatment of brain wounds The histological appearance of preparations did not suggest that the application of proflavine caused any alteration in the normal processes of inflammatory reaction and healing

Using buffered isotonic proflavine sulfate emulsion as an occlusive emollient dressing for superficial granulating areas and second degree burns, Heggie et al (85, 86) found no inhibitory action on fibroblastic activity and epithelialization in the healing process They found the acridines most useful

Proflavine is of greater value than sulfanilamide and is at least as good as sulfathiazole in the local prophylaxis and treatment of Cl welchii infection in mice (68) The authors recommend its further use and testing as a wound dressing The article of Mitchell and Buttle (69) recording their results with flavines in the North African Campaign shows that proflavine is much less toxic than acriflavine It was used in 80 cases with beneficial results in every case Where staphylococci are the infecting organisms, proflavine proved more efficient in controlling or eliminating infection than any other drug so far tried, and many cases of mixed infection responded very well With one exception, no interference with healing was noted Most patients found the dressings painless Sulfonamides were of little value on wounds which were deep or extensive, particularly those involving bone or joint where mixed infections are the rule Various forms of treatment were tried including plain saline and vaseline dressing, hypertonic salt, urea, eusol, acriflavine, gentian violet, brilliant green, hydrogen peroxide, glycerine and sulfonamide solutions, blood transfusion, etc A number of cases failed to respond despite everything tried, and this led to the use of proflavine From 0 5 to 2 0 grams of proflavine were placed directly into the wound As was previously reported, B proteus was most resistant to proflavine

5-Aminoacridine hydrochloride was tested (70) by Russell and Falconer and found to cause no appreciable damage to the brain when applied in concentration of 1 in 1,000 In its action on tissues it is close to proflavine or 2 7-diaminoacridine When applied as a powder directly, all three agents were destructive not only to the brain but also to muscle and other soft tissues These workers feel that it is inadvisable to apply the powders directly to wounds They discuss the results of Mitchell and Buttle (69) and feel that the wounds were heavily infected which fact resulted in the beneficial effects The use of combined

sulfonamide and proflavine is recommended Beath (71) has recently proposed the use of proflavine sulfate at 0 1% for the suppression of infections in wounds Browning (72) states, "It has been shown under experimental conditions that the flavines, when applied to the tissues at the site of inoculation are highly effective in preventing the development of infection with various organisms including streptococcus and certain gas gangrene anaerobes" This statement made in March, 1943, included a warning to the effect that the continued use of flavine retards granulation and healing, and recommends the use of other treatments after the initial treatment with flavines Browning feels that the most important point practically is the capacity of the flavines to prevent and control infection This so called pickling or cold storage effect has enabled wounded men to be transported without redressing

Before concluding the discussion of acridine chemotherapy, it is in order that results with a few of the more complex acridines should be mentioned Friedeman (99) reported on the use of three of the compounds prepared by Schnitzer and Silberstein (13) He used 3-ethoxy-8-nitro-5-diethylaminooxypropylamino-acridine, 3-diethylaminoethoxy-8-nitro-5-aminoacridine and 3-ethoxy-8-nitro-5-glycyldiethylaminoethylamidoacridine in cases of pleural empyema and found them to be most effective Rivanol (7) enjoyed some success in the clinics This compound is 3-ethoxy-5,8-diaminoacridine

To summarize or draw conclusions from this conflicting literature is a process requiring caution It must be done largely on the basis of an evaluation of the methods used by the various investigators The author is inclined to concede to Mitchell and Buttle (69) that their practical experience outweighs all other evidence They have had an opportunity to use pure chemicals under the most severe conditions Adverse reports are largely based upon in vitro considerations of effect on leucocytes or fibroblasts, etc , which do not necessarily reflect in vivo conditions Items of importance are the necessity of using an excess of flavine over that needed for direct application if dressings are used, as the dressings adsorb the flavine The concentration to be used is 0 1% buffered to pH 6 2 in isotonic saline Prolonged application seems to be contraindicated

CHEMOTHERAPY

Tumors

Gye (47) found that the action of acriflavine in vitro on the filterable agent which causes the Rous sarcoma of birds is closely similar to that on the virus of bovine pleuropneumonia He concluded that this was strong evidence that the tumor agent belonged to the virus group of disease producing microorganisms On transplantable mammalian tumors, Mellanby (48) found that the acriflavine produced the same effects as on filterable tumors of birds A concentration of the antiseptic which produced changes in one produced changes in the metabolic activities of the other There was a marked and irreversible reduction of oxygen uptake without change in the glycolysis The mammalian tumor so treated lost the power of growth, while the bird tumor retained it From this and other

chemical observations it appears that the mechanism of inducing growth of the mammalian tumor depends on cells more or less intact as regards their metabolic properties, more particularly those which allow the uptake of oxygen In 1941 Lettré (49) reported that trypaflavine inhibits complete mitosis 0 025 and 0 05 mg were given on 5 successive days, and this treatment prevented the development of the tumor and prolonged the life of the test animal Higher doses of the acridine further prolonged the survival period of 14 days for the controls to a period in excess of 31 days for the experimentally treated animals

PHARMACOLOGY

Anaphylactoid reaction following the administration of 250 mg of acriflavine was noted by Treuherz (73) This was due to a fall in blood pressure demonstrated to occur in the dog (74) Severe pathology was seen in the liver and kidneys of these dogs Crittenden (75) found little alteration in blood pressure, heart rate or respiration unless large doses of acriflavine were used He reported that various preparations of acriflavine showed marked differences in pharmacological properties due to chemical impurity Suffolk (76) reported that in bacteriostatic concentrations acriflavine produces no toxic effects on the isolated frog heart The dye prolonged rather than shortened the survival period Seventeen acridine compounds were tested and only one, a chloro compound, was toxic The majority of the chemicals of the acridine series antagonized acetyl choline Some compounds, acriflavine and atebrine, showed this action with frog tissue and mammalian tissues Suffolk could find no direct correlation between pharmacological properties and chemical structure He recorded a surprising contract between 2 aminoacridine and 4-aminoacridine, both had a similar depressant action on the auricle but in antagonism to acetyl choline the former is more powerful than any other compound while the latter is inert The four diaminoacridine sulfates showed no power to antagonize acetyl choline, thus differing from the hydrochlorides The aminoacridine compounds are but additional members of a long list of diverse compounds which antagonize acetyl choline and thus antagonize the action of the parasympathetic nerves Clinical experience has demonstrated that no actual interference with parasympathetic activity occurs despite the fact that blood concentration is attained which might give such an effect

TOXICITY

Acriflavine in the form of 0 1 and 0 5% solutions has been used intravenously in human beings in doses of 200 mg with no evidence of toxicity (77) There are, however, several reports (77, 78, 79) of the precipitation of acute toxic hepatitis, as manifested by jaundice, following the use of acriflavine The cases reported by Hanschell (79) followed the use of 0 78 grams In all his cases, jaundice was well marked and was catarrhal in type with enlargement of liver and, in one case, of the spleen The onset was delayed for 112 days, and the duration was 16 days Cullinan (78) reported only one case, which had received 10 grams of acriflavine The patient died and his liver showed histologically a

typical acute toxic hepatitis Before death jaundice, vomiting, drowsiness and coma characterized the syndrome Birch (77) noted some jaundice but felt that within therapeutic limits the danger of toxic hepatitis from acriflavine per os was negligible

In the rabbit, acriflavine is destructively organotropic, particularly against liver and kidney (97) Many of the clinical investigations have indicated that the compound is irritating to the mucosa of the gastrointestinal tract (98) causing nausea Young-Simpson (80), an enthusiastic supporter of the use of flavine, circumvented the intestinal irritation by using enteric coated tablets

The toxicity of acridines, mainly acriflavine, for leucocytes is a subject considered in the section on chemotherapy It need be stated here only that while the work is controversial, acriflavine is probably capable of inhibiting phagocytosis in concentrations around 1 in 2,000 (81)

The most important piece of work on the relation between structure and toxicity in the acridine series of chemotherapeutic agents is that of Albert, Dyer and Linnell (9), who report that the entry of 2-amino substituent into acridine is found to decrease the toxicity which is further modified by the introduction of the second amino group, the direction of the modification depending on the position of the second entering group 4-aminoacridine differed from all other derivatives in giving rise to tetanic spasms Acriflavine was considerably more toxic than proflavine The substitution of an amino group of acridine by a chlorine atom led to increased toxicity Placing of two amino substituents in one ring led to a notable heightening of toxicity The acetylation of one of the amino groups in proflavine reduced toxicity, a similar effect being obtained by the conversion of the acridine nucleus to the corresponding acridone structure 2 7-diaminoacridine which has only two-fifths of the toxicity of proflavine and one-tenth that of acriflavine, while possessing the same order of antiseptic potency, is recommended for further trial

The effect of acriflavine on blood is interesting The work is questionable because of its vintage and should be repeated Bohland (96) noted that one hour after the intravenous injection of trypaflavine into the circulation, the number of erythrocytes is reduced by half a million and white blood cells are increased by one-half or even doubled The number of lymphocytes showed the greatest increase Meleney and Zau (97) believed that the leucocytosis observed in rabbits after the intravenous injection of neutral acriflavine was proportional to the amount of dye injected Little effect on red cells or on clotting and bleeding time was noted

STRUCTURE AND ACTIVITY

The work of Browning et al (82, 83) and more recently that of Albert and Linnell and their school (8, 9, 22, 12) has been outstanding in this field In 1921, Browning and Cohen (83) investigating modification of the acriflavine molecule, reported that introduction of methyl radical into the basic nucleus increased potency. Substitution of methyl, by ethyl, propyl, isobutyl, isoamyl, phenyl or benzyl had almost no effect on antiseptic properties Langer (84), however, felt that there was little difference between acridine and acridinium compounds

Continuing his studies, Browning (82) found that no fragment of the acridine molecule equalled or even approximated closely the diaminoacridines The amino group enhanced the antiseptic potency both for staphylococci and coli The chloroacetate, chloropropionate and chloracetanilide derivatives in which these radicals substituted for the methyl differed little in potency Introduction of methyl and ethyl groups into the amino radical depressed rather than enhanced the antiseptic potency Substitution of one amino group hydrogen by acetyl radical practically abolishes the antiseptic action Carboxylic esters were so weak as to suggest a depressing action by carboxyl on antiseptic potency Replacement of amino groups by hydroxyls almost eliminated antiseptic power Of all pyridine, quinoline and phenazine compounds tried, only two were equal to the acridines, namely, 2 7-tetramethyldiaminophenazine and 2 7-diamino-3,6-dimethylphenazine Morgenroth (7) worked with a 5 aminoacridine series in which the 3 position carried an alkoxy grouping If the 5-amino group was substituted, the potency was diminished materially 5-aminoacridine has come into prominence recently because of its non-staining quality (12) When an amino group was put in the 8 position, maximum efficiency was attained This compound became known as rivanol Hata (5) experimented with methoiodide compounds similar to acridine, a methochloride compound, and found them to be less toxic and equally bactericidal to the corresponding methochloride

1-aminoacridines (8) are totally inactive The explanation of this lies in hydrogen bonding as outlined in the section on chemistry A 2-amino substituent increases activity which is further enhanced by a second amino group in the 2, 3, 4, or 5 positions in the other ring, accompanied by increased toxicity in the case of a second 2 substituent When two amino groups are present (3 7) the activity is moderate, but the 3 8 diamino acridine is as active as proflavine although of lower toxicity, a 4-amino substituent has small activity while the 5 position is highly active but may give rise to increased toxicity Intact acridine nucleus is essential The 2 chloro-5 aminoacridine is interesting Two series of amino group compounds in 2 and 3 position were made with the chlorine in 6, 7, 8, 9 In general, the chloro compounds were slightly less active against B coli and Strep pyogenes than the parent amino compound Thus the chlorine atom did not increase the activity of the amino compounds as it does in the chlorophenols On the other hand, 2-amino 6-chloro, 2-amino-7-chloro and 2-amino 8-chloroacridines were much more active against Staph aureus than were the parent amino derivative or proflavine itself This result is of importance as the acridines are generally not very effective against Staph aureus The series of chloroalkoxy derivatives was prepared and examined but little difference in activity was observed according to position of substituents The series was insoluble and of little interest 2 7-diaminoacridine was ten times less toxic than acriflavine

SUMMARY

Much of the work done before 1910 and some since that date was complicated by the use of impure chemicals This is a point which can not be too strongly emphasized as the flavines are difficult to obtain in a pure form Work done on

fibroblast and leucocyte destruction in the test tube is not necessarily a true reflection of the value of a chemotherapeutic agent in practice It can only be said at the present time that a great deal of research must be carried out with these agents before conclusions can be reached

It is the opinion of the reviewer that the acridine series offers limited potentialities as systemic disinfectants As local and superficial antiseptics, however, they offer excellent potentialities The most promising members of the series, 5-aminoacridine and 2.7-diaminoacridine, have not been subjected to any significant amount of clinical trial In fact, their use in experimentation in the laboratory is quite recent 5-aminoacridine seems to offer the greatest hope as it is a non-staining chemical and, therefore, could be applied through dressings Acriflavine has been generally discredited, but it is possible that much of the discredit is undeserved Acriflavine as such has been justifiably supplanted by proflavine, 2 7-diaminoacridine and 5-aminoacridine The recently introduced (19) proflavine dihydrochloride offers advantages over proflavine sulfate

The appearance of organisms resistant to sulfonamides makes imperative the further consideration of chemical agents of the type of the acridines The work of Mitchell and Buttle (69) carried out under adverse conditions demonstrates conclusively in the reviewer's opinion the fact that the acridines are valuable chemotherapeutic agents

The sulfonamides, the anti-biotics, the acridines, the diamidines and all other known chemotherapeutic agents represent but the beginning of the ever expanding armamentarium of the physician Pantoyltaurine (88), the metabolic analogue of pantothenic acid, represents the first of a new series We must expand the horizons and explore fields already discovered

The British Medical Association (103) has editorially stated that the reason for the failure of the acridines in the past was due to "wrong choice of compound and misapplication " They further state, "It (proflavine) should certainly be given further trials in comparison with other agents for the prevention and treatment of wound infections " The American Medical Association (102) concurred when it stated editorially, "The scarcity of penicillin and certain limitations of the sulfonamides make it desirable to investigate further the possibilities of the acridine compounds, in particular proflavine "

ADDENDUM

Four articles of great merit have appeared since this review went to press Mitchell and Buttle (Lancet, **2**, 287, 1943) find diflavine (2 7-diaminoacridine monohydrochloride) and proflavine to be less toxic than 5-aminoacridine Among battle casualties with wounds of every type of severity, beneficial results were obtained in 250 cases Both diflavine and proflavine were effective against streptococci, staphylococci and clostridia, but they gained the impression that proflavine was the better drug The diflavine was used by dusting 0 5 to 0 75 grams onto the wounds after cleansing the wound with 1/1000 proflavine In 5% solution in glycerine, diflavine was applied as a non-adherent dressing Using this procedure, wounds were redressed every fourth or seventh day Proflavine

produced striking improvement in two cases where succinylsulfathiazole had failed and in one case where penicillin had been given a fair trial The use of proflavine base and sulfanilamide powder in the proportion of 0 25 grams to 5 grams is recommended by Brownlee and Tonkin (Quart J Pharm and Pharmacol, **16**, 73, 1943) McIntosh and Selbie (Lancet, **2**, 224, 1943) also recommend a mixture consisting of 1% proflavine in sulfathiazole The mixture was effective against all organisms causing gas gangrene and had the added advantage of diminishing the local toxic effects of proflavine An excellent study of the acridines by Ungar and Robinson (Lancet, **2**, 285, 1943) resulted in their recommending 2 7 diaminoacridine as being less toxic and less apt to interfere with healing

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NEUROFIBROMATOSIS (VON RECKLINGHAUSEN) AND OSTEITIS FIBROSA CYSTICA LOCALISATA ET DISSEMINATA (VON RECKLINGHAUSEN)

A Study of a Common Pathogenesis of Both Dysplasias. Differentiation between "Hyperparathyroidism with Generalized Decalcification and Fibrocystic Changes of the Skeleton and Osteitis Fibrosa Cystica Disseminata

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Introduction. F. von Recklinghausen first described the clinical syndrome known since as neurofibromatosis in an article "Ueber die Neurofibrome der Haut und ihre Beziehungen zu den Neuromen," in an Anniversary Volume in honor of R. Virchow's 60th birthday in 1882. Ten years later, the same author dedicated to R. Virchow's 70th birthday a second article entitled "Die fibrose oder deformierende Ostitis, Osteomalacie und osteoplastische Carcinose." In the latter article he described the clinical syndrome thereafter known as "osteitis fibrosa cystica." Recklinghausen quotes other authors as having reported cases which might be identical to the features of osteitis fibrosa cystica (Bronlep 1842, J. Engel 1864, Wilks 1869, Langendorff and Mommsen 1877, Hirschberg 1889). He did not himself attribute a common etiology to these two separately described syndromes. He did not describe any pigmentation of the skin or involvement of other organs such as the meninges, brain, skeleton, or viscera.

The French school (P. Marie and H. Bernard, A. Chauffard) first called attention to the pigmentary anomalies of the skin in neurofibromatosis, while the visceral and bone changes were first reported in the German, English, and American literature (Adrian 1901, Bloodgood 1904, Silver 1911, Flinsbe 1914, Barne 1918, Stahnke 1922, Brooks and Lehmann 1924, Fliegel 1935, Stalmann 1933, Scherer 1933). Later publications (for literature see Morton 1922, Stenholm 1924, Nothmann 1937, Falconer and Cope 1942) mentioned osteitis fibrosa cystica as a separate nosologic entity, both clinically and anatomically. Fliegel (1925) and Stalmann (1933) called attention, however, to the similarity of the fibrous bone cysts occurring in neurofibromatosis and osteitis fibrosa cystica. Studies have been published in the English, French, and Italian literature which show that cutaneous neurofibroma, café au lait spots, and osteitis fibrosa disseminata may occur in the same patient.

These observations, however, were overshadowed by those of the Viennese surgeon, F. Mandl, who in 1926 first reported a successful extirpation of an adenomatous parathyroid gland on a patient suffering from osteitis fibrosa cystica. Collip's physiological studies (1925) of the hormone of the parathyroid gland had already demonstrated that an excess of this hormone causes an in-

[1] Aided by grants from the Rockefeller Foundation and the Godfrey Hyams Trust Fund.

crease in the calcium level and decrease in the phosphorus level of the serum At the same time a demineralization of the entire skeleton takes place, whereby an overflow of calcium mobilized from the skeleton through the kidney may be observed Also, calcium deposits, so-called calcium metastases, may be produced by continuous injection of parathyroid hormone Fibrous tissue replaces the bony trabeculae and becomes soft, in some areas forming cyst-like structures (Mandl, Jaffe)

These experimental discoveries and the operative success of Mandl gave rise to the idea that the pathogenesis of osteitis fibrosa cystica may entirely depend upon the correct function of the parathyroid glands This belief was strengthened when an hypertrophied or adenomatous parathyroid was found, together with high serum calcium and low serum phosphorus levels, in patients suffering from osteitis fibrosa cystica (Dubois, Bauer, Albright, and Aub, Bart and Bulger)

Since publication of these findings, osteitis fibrosa cystica has been commonly regarded as a result of hyperparathyroidism despite the fact that many cases of the disease described more recently have shown neither parathyroid enlargement, increased calcium levels in the serum, generalized demineralization of the entire skeleton, nor calcium metastases But many of the newer papers dealing with osteitis fibrosa cystica do report the coincidental occurrence of large pigmented blotches Fuller Albright took account of this discrepancy when he proposed a distinction between osteitis fibrosa cystica disseminata and osteitis fibrosa cystica generalisata, in which he restricted the name osteitis fibrosa disseminata to the cases in which localized and disseminated lesions of the skeleton are present, together with normally calcified and normally structured bones In these instances normal calcium and phosphate and only slightly increased phosphatase values are found On the other hand, he reserved the designation osteitis cystica generalisata for the cases of generalized demineralization of the skeleton, with fibrocystic lesions and high calcium and low phosphorus levels together with high phosphatase values In these cases enlargement of at least one parathyroid gland has been found on exploration

The term "polyostotic or monostotic fibrous dysplasia of bone" is used by L Lichtenstein and H L Jaffe (1942) in their extensive histological studies of osteitis fibrosa cystica disseminata A deep-rooted congenital anomaly of development is considered by these authors to be the primary etiological factor

This present study endeavors to clarify the pathogenesis of osteitis fibrosa cystica localisata and disseminata (von Recklinghausen) An attempt will be made to demonstrate that under the heading of osteitis fibrosa cystica Recklinghausen, two etiologically different clinical entities are reported One, osteitis fibrosa cystica disseminata, will be shown by collected evidence to be related by its clinical and histological features to neurofibromatosis (Recklinghausen) The other, hyperparathyroidism with resulting fibrocystic bone lesions, is primarily caused by hyperfunction or adenoma of one or more parathyroids Parathyroid hyperactivity may also, as a secondary reaction, complicate different kinds of malacic bone diseases (osteomalacia, senile osteoporosis, multiple myeloma,

secondary carcinomatosis of the bones) In rare instances, it may also complicate severe cases of osteitis fibrosa cystica disseminata

The material to be discussed, collected from the literature with the addition of our own cases, will be presented in six separate sections

I The Pathogenesis of Cutaneous Neurofibroma
II The Significance of Pigmented Areas (Taches du Café au Lait or Geographical Map-Like Brown Blotches) in the Diagnosis of Neurofibromatosis
III Fibrocystic Bone Lesions in Neurofibromatosis
IV Hyperparathyroidism with Generalized Decalcification and Fibrocystic Lesions of the Skeleton, and Osteitis Fibrosa Cystica Disseminata Two Different Clinical and Pathogenic Entities
V The Pathogenesis of Osteitis Fibrosa Cystica Localisata and Disseminata (Recklinghausen)
VI Endocrine Symptoms in Neurofibromatosis and Osteitis Fibrosa Cystica Disseminata (Recklinghausen)

I THE PATHOGENESIS OF CUTANEOUS NEUROFIBROMA

Since the publication of von Recklinghausen's original paper, "Ueber die Neurofibrome der Haut und ihre Beziehungen zu den Neuromen," there has been much controversy as to whether these neuromas develop from mesodermal or ectodermal tissue In Virchow's classification of tumors they were grouped as false neuromas because of their lack of nerve cells The nodular fibromas, or fibroma molluscum, which rise above the skin in many cases, are purely fibromatous and do not show any connection with nerve tissue For this reason the famous French neurologist, Pierre Marie (1896), doubted the correctness of Recklinghausen's original concept of neurofibromatosis As early as 1896, A Chauffard, whose opinion was based upon the histological studies of F Ramond, suggested replacing the name "neurofibromatosis" with the designation "fibromatose pigmentaire" He admitted, however, that "two categories of fibromas analogous in their clinical appearance but different in site and origin must be distinguished" His two categories were as follows (1) Fibromas originating with the perineural tissue and accompanied by multiple neuromas of the nerve stem or its branches, and (2) Fibromas which do not originate in the perineural tissue and are not accompanied by multiple neuroma In both instances pigmented spots of café au lait or deep "brunatre" color may occur The pigmented blotches are, according to Chauffard, as characteristic of the presence of neurofibromatosis as the nodular fibroma itself
the nodular fibroma itself

On the basis of the often-observed hereditary factors, Adrian (1901), Preiser and Davenport (1918), and also Kaufmann (1921) claimed that a deep-rooted anomaly of the "anlage" of the germinal layer results in this type of growth, where ectodermal and mesodermal elements may alternately prevail

In contradiction to this dualistic explanation of the neurofibromas, which classified them as perineural or purely fibromatous, Verocay (1910) and Pick

and Bielschowsky (1911) demonstrated that the neurofibromatous nodule originates from the sheath of Schwann, even if the large fibromatous new growth does not show any connection with the neural tissue and seems to be a purely fibrous new growth Most authors since then have agreed with this explanation of the genesis of the variety of new growths included under the designation neurofibromatosis von Recklinghausen (Lhermitté and Leroux, Siemens, Roussier and Cornil, Roussy and Oberling, Cornil, Kissel, Beau, and Alliez, Scherer) Even for the elephantiasic hyperplasia of the connective tissue of the skin the neurofibromatous etiology is accepted, and it is of importance in connection with our later discussion of osteitis fibrosa cystica to note that cyst formation also occurs in this elephantiasic skin fibroma (Carrière, Huriez, Gervois, and Dupret 1938) These authors suggested replacing the name neurofibromatosis with the designation "glioflbromatosis Recklinghausen" Murray and Stout (1940) demonstrated by tissue cultures of the normal nerve sheath that Schwann cells can and do condition the formation of collagen without the intervention of fibroblasts The results of these experiments are not in conformity with the opinion expressed by F B Mallory as well as that of Penfield, that collagen and reticulin can only be formed by cells of mesodermal origin

The extensive and excellent histological studies of P Masson (1942) finally offered definite histologic evidence that neurofibroma derived from the Schwann symplasm of neurofibromatous fascicles, which acquire autonomic fertility of blastomas He showed that "the adult schwannoglia, normally stable in the full-grown nerve fiber, possesses a latent fertility, in a way constitutional, which may be stimulated into activity by any alteration of its associated neurite The early schwannogliomas appear as localized swellings of the neurofibromatous fascicles These swellings are made of the Schwann strands of the fascicles, which grow lengthwise, become cylindrical, undergo a longitudinal partitioning, and are rolled cylindrically around the primitive fascicular axis If this axis persists, the ball may become very large On section its elements appear as a *large whorl around a central point* In the normal histogenesis of the nerve, the embryonic schwannoglia builds up the nerve around the neurites In the regeneration of the adult nerve, the schwannoglia regenerates the nerve with the neurites In its *aneuritic proliferations* the schwannoglia builds up neuroid structures without neurites In the encapsulated tumors, the schwannoglia builds up unequilibrated nerve structures, poorly neuralised and mostly aneuritic The fact that the neurofibromas belong either to Recklinghausen's disease or to Gombault-Mollet's disease,[2] both hereditary, favors their dysgenetic origin, and suggests a very early dysgenesis of the neural crests In the neurofibromas the initial lesions conditioned by this dysgenesis are the alterations of the neurites, followed by schwannian proliferations Their fertility seems to be the one important constitutional feature of the schwannoglias In the schwannogliomas there is something more *the schwannoglial fertility appears as a new property* It seems to be autonomous, blastomatous"

The fact that the schwannoglia is able to build up purely neurotised and even

[2] Familial progressive hypertrophic neuritis

entirely aneuritic fibromatous tumors is of great importance in explaining the occurrence of pure fibromatous growth in neurofibromatosis without demonstrable nerve tissue within the fibroma Gruber explains the aneuritic fibrous growth in neurofibromatosis as an "induced growth" The meaning of growth by inducement and of Masson's term "fertility" of the Schwann syncytium, whereby the nerve fiber may disappear and may not be any longer demonstrable in the fibrous growth, is identical This phenomenon is of especially great significance in connection with interpretation of the pathogenesis of neurofibromatous growth in other organs than the cutaneous tissue It is understandable that a neurofibromatous growth will interfere with the structure of such an organ and vice versa, i e, if an organ such as an osseus structure undergoes a constant ana- and katabolism of its mineral components, it may be expected that the histological pattern of the fibromatous growth will be interwoven with the features of regeneration and resorption of the bony structure The disturbance of bone formation and resorption may even be so great that the fibromatous involvement of various parts of the skeleton may erroneously be considered as a primary bone disease Such possibilities will be considered in the discussion of neurofibromatous involvement of the skeleton and osteitis fibrosa cystica disseminata

Summary The investigations of Masson have demonstrated that fibromas in neurofibromatosis may no longer show their derivation from the schwannogha by the presence of nerve tissue within the fibromatous masses The lack of nerve tissue in fibromatous masses therefore does not disprove their neurofibromatous origin The finding of aneuritic fibromas in other organs than the skin, together with neurofibromatous involvement of the skin, is highly suggestive of a common histogenesis for the two features Whorls of spindle cells, if present in the fibrous tissue, indicate the neurofibromatous origin of the involvement

II THE SIGNIFICANCE OF PIGMENTED AREAS (TACHES DU CAFÉ AU LAIT OR GEOGRAPHICAL MAP-LIKE BROWN BLOTCHES) IN THE DIAGNOSIS OF NEUROFIBROMATOSIS

Brown blotches, "taches du couleur, cafe au lait," or deep "brunatre," and large areas of pigmentation are the most common features of neurofibromatosis Recklinghausen Chauffard (1896), Weber (1909), Stalmann (1933), and also Siemens (1926) reported their occurrence in almost 100 per cent of their neurofibromatous cases Pigment anomalies may appear as small round spots, ellipsoid brown spots, or irregular but sharply contoured indented plaques of deep brown or café au lait coloration The area involved may range from the size of a pea to large regions of pigmentation with sharp borders The pigmented spots are usually not congenital and may develop in childhood or later life

The sharp borders of the pigmented areas in neurofibromatosis contrast, according to Siemens, to the fuzzy contours of pigmented blotches, the so-called "naevi spili" The latter are usually congenital and are not a sign of neurofibromatosis A few single verrucous naevi may be present in neurofibromatosis, but they are not a characteristic feature of the disease

Histological examination of café au lait or deep brown pigmented spots shows the pigment to be located in the basal layers of the epidermis as true melanin, as in the skin in Addison's disease The increased pigmentation in both instances is brought forth by the same medium, namely the nerve tissue, the cause, however, is different In Addison's disease it is the deficiency of a hormonal agent which normally balances the melanin production of the epidermis via cutaneous nerves In neurofibromatosis it is a localized anatomical anomaly in the cutaneous nerve itself producing the increase of melanin in the epidermis

The café au lait spot is, according to Stalmann, the first reaction of the skin to structural changes of the finest subcutaneous nerve-endings characteristic of Recklinghausen's disease The finest branches of the subcutaneous nerves show thickening and clubbed expansion of the fibers Often an increase of fibrous tissue around or in the course of the nerves will be visible under the microscope The increase of the fibrous tissue may lead to encapsulated solid fibrous masses which adhere tangentially to the nerve, or there may be no relation at all of the fibrous growth to the nerve tissue itself Sometimes an ingrowth of a single nerve fiber or rests of atrophic demyelinated fibers are microscopically demonstrable between the fibrous tissue The intimate relationship of deep brown pigmented blotches to the structural changes of the underlying subcutaneous nerves is most conspicuous in cases of plexiform neuromas The ramified vermiform fibrous tumors of the subcutaneous nerves are often directly connected with pigmented blotches of the overlying skin (Stalmann, Carrière and Huriez, Gruber) In cases of osteitis fibrosa cystica disseminata in which the osseous system is involved on only one side of the body, the brown spots are found frequently on the skin of that same side This phenomenon gives weight to the assumption that both features, brown spots and osseous fibroma, are connected by a common pathogenetic principle, i e neurofibromatosis.

The pigmented spots may be the only manifestation of neurofibromatosis In such cases, the so-called "forme fruste," the presence of the café au lait spots is sufficient for the diagnosis of neurofibromatosis in the terminal filaments of the subcutaneous nerves (Weber, Wise and Ellen, Leader and Grand) Where café au lait spots are found one should search for hidden involvement of other organs, especially for lesions of the bone

Summary Pigmented areas of skin with sharp borders (café au lait spots or geographical map-like brown blotches) are the result of structural changes of the underlying smallest skin nerves The term "forme fruste" is used for cases where the pigmented areas are the only visible manifestations of neurofibromatosis Pigmented blotches of the café au lait or geographical map-like variety are as much an indication of neurofibromatosis as the cutaneous neurofibromatous nodule itself

III FIBROCYSTIC BONE LESIONS IN NEUROFIBROMATOSIS

The French school (Carrière, Huriez, Gervois, Dupiet) considers neurofibromatosis of Recklinghausen to be a clinical syndrome which may manifest

itself in different organs simultaneously or which may occur only in one or another organ of the body They distinguish between

(1) A cutaneous syndrome with tumor formation and pigmentation (un syndrome cutané, tumoral et pigmentaire)

(2) A nervous system syndrome involving the brain or the peripheral nerves (syndrome nerveux, central et périphérique)

(3) A visceral syndrome with and without tumor formation, and with giantism of the intestinal organs (syndrome tumero-viscéral)

(4) An osseous syndrome (syndrome osseux), including pseudarthrosis in childhood, kyphoscoliosis, giantism of one bone, periosteal lesions, fibroma and cyst formation of bone

(5) An endocrine syndrome (syndrome endocrinien)

Our present purpose is to discuss the possibility of an etiological relationship between the fibrocystic lesions of the bone occurring in Recklinghausen's neurofibromatosis and the enormous fibrocystic masses replacing the trabecular tissue of the bone in osteitis fibrosa cystica localisata and disseminata, also described by Recklinghausen For this purpose we wish to restrict the scope of the discussion to one part of the osseous syndrome in neurofibromatosis, namely to the fibrocystic manifestations in the skeleton

Recklinghausen himself was not aware that fibroma with cysts may also occur in the bones in the disorder which he designated as neurofibromatosis Bone cysts in the long bones have been described in the liberature for many years It is not surprising that most of these observations have been recorded in the surgical literature, because such patients come under observation of surgeons for fractures and complaints of their static and locomotor facilities It is, however, astonishing that these so-called cysts, which even in the earliest observations were found to be no real cysts but fibromas with secondary cyst formation, were not recognized as related to neurofibromatosis

The appearance of single bone cysts of the large bones in Recklinghausen's neurofibromatosis was first demonstrated by Brooks and Lehman In their important paper it was shown that the bone cysts in Recklinghausen's disease are not only of cortical or subperiosteal location, but they are also found in the trabeculated areas of the long bones Case I of these authors had neurofibroma and pigmented areas of the skin, and bone changes consisting of subperiosteal cysts as well as isolated cysts in the long bones The evidence of the occurrence of both varieties of bone cysts in one patient is of particular interest because it is claimed in the roentgenologic literature that only the subperiosteal cysts are characteristic of Recklinghausen's neurofibromatosis Many observers (Fliegel, Stalmann, Lehman, Leader and Grand) have shown that in Recklinghausen's neurofibromatosis fibromatous cysts of different locations occur, varying from central and periosteal cysts to pedunculated and subperiosteal fibromas It seems that the finding of one or several isolated bone cysts is as suggestive of the existence of Recklinghausen's neurofibromatosis as the presence of an isolated neurofibroma of the skin or of one or more café au lait spots

Adrian (1901) and even before him Koenigsdorf, Marie, Hoisnard, and Haus-

halter mentioned that the bony changes in neurofibromatosis may result in softening of the bone Fliegel (1925) describes bone changes in neurofibromatosis consisting of cystic as well as fibrous malacic opacities of the skeleton He suggests that bone changes in neurofibromatosis and osteitis fibrosa may be connected by similar etiology. Indeed, the clinical features of Recklinghausen's neurofibromatosis and localized and disseminated osteitis fibrosa cystica may be so similar that cases described in the literature as Recklinghausen's neurofibromatosis with bone changes could also have been published as osteitis fibrosa cystica (Gould, Cases 1 and 4, Stalmann, Cases 2, 3, 4, 23, 27, Ashton, Uhlmann and Grassmann, Merklen and Israel) And conversely, cases described as osteitis fibrosa cystica could be called neurofibromatosis Recklinghausen with bone changes (Marinte and Maciel, Cohen and Douady), because in these instances pigmentation, café au lait spots, or geographical map-like brownish pigmented areas occurred as well as cutaneous neurofibromata

This similarity of clinical symptomatology makes it seem possible that both diseases have been confused in the literature In Section V will be discussed whether both diseases are not in reality based on the same pathogenetic principle, neurofibromatosis with fibrous bone cysts being a milder manifestation and osteitis fibrosa cystica disseminata being the most extensive form of the same condition

On x-ray examination of the so-called cysts, an area of lesser density of the bone is seen, very often oval-shaped, or else conglomerated small areas of lesser density giving the impression of a loculated multicameral cyst Sometimes the density of the surrounding area of the bone gives the impression of a bony shell, especially in the cysts which are found in the subperiosteal space Roughening and irregularities of the periosteum are sometimes observed in the same case Expansion of the cortex overlying the area of lesser density may or may not be evident, according to the location of the process

Only a few histological examinations of fibrocystic bones have been reported (Brooks and Lehman, Turnbull, Uhlmann and Grassmann) The structure of such cyst-like formations of the bone varies Fibrous tissue prevails, but osseous or even cartilagenous elements are also found In smaller areas cystic softening may be present The area of lesser density of the bones observed in x-ray pictures is mainly due to replacement of the bony structures by fibrous tissue and to a lesser extent to real cyst formation The cellular elements consist of small, slender, spindle cells, often in a palisade effect with the nuclei arranged in parallel and longitudinal rows It must be emphasized that real nerve structures are not found in the bone fibroma in Recklinghausen's neurofibromatosis The main characteristic, however, of such fibrous tissue seems to be the "whorl of cells" (Uhlmann and Grassmann) dispersed in fibrous tissue These "whorls of cells" are, according to Masson, most characteristic of neurofibroma In the beginning the whorls develop around a myelinated fiber The nerve fiber, however, disappears in later stages and only the whorls of spindle cells remain On the basis of this conception, the "whorl of cells" or the "turbillions" of cells are the hallmarks of neurofibromatosis, suggesting its nerve origin Even if only fibrous tissue remains, a whorl arrangement of cells signifies the original presence of schwan-

noglial fascicles from which the fibrous tumor originated, or was induced, as Gruber expressed it

The pathological process of bone involvement is not stationary and quiescent, more extensive tissue changes occur The shaft of the bone may become soft and plastic, or bowing and spontaneous fractures of the bone may result The growing fibrous tissue may locally expand the bone until only a fine shell of bony cortex remains The fibrous tissue itself may undergo a collagenous or myxomatous change with, occasionally, true cyst formation containing a brownish fluid as a result of bleeding within the growth

Summary Fibrocystic involvement of localized areas of the skeleton, especially of the long bones but also of other portions, occurs in neurofibromatosis together with café au lait spots and cutaneous neurofibromas Osseous fibromata are not only found as so-called "subperiosteal cysts," but also as fibromata located in the trabeculated spaces of the long bones The microscopic examination of the osseous fibroma does not reveal nerve structures within the fibroma, but whorls of spindle cells are in some areas found as "hallmarks" of its neurofibromatous origin

Cases Illustrating Neurofibromatosis, Café au Lait Spots and Small Fibrocystic Bone Lesions *Case I* S S (No 3173) entered the Joseph H Pratt Diagnostic Hospital (unit of the New England Medical Center) in February, 1937 The patient was a mentally backward boy of eighteen years, and the history was largely obtained from his eldest brother He was born normally but was underweight as an infant There was no abnormality in early development except for the fact that he was always mentally retarded His mother stated that he was meek, truthful, and obedient At the age of eighteen he was still treated as a child

In 1935, his testicles were descended operatively, but they did not remain in the scrotum Antuitrin-S was given without effect It was learned that both his mother and a sister had areas of skin pigmentation and definite evidence of neurofibromatosis

On admission he was rather obese, weighing 102 pounds with a height of 4 feet 8 inches He gave the appearance of a ten-year-old mentally retarded child There was no axillary or pubic hair The subcutaneous fat was considerably increased, the mammae definitely overdeveloped The skin was dry Numerous café au lait spots were scattered over the body On the back of the head in the occipital region there were small subcutaneous nodules, two on each side of the occipital region were movable under the skin and later were proved histologically to be neurofibromatous nodules The pupils reacted to light and on accommodation The eye grounds showed pale disks The vessels were tortuous, especially on the right side Visual fields were normal, eye movements normal The teeth were in good condition The thyroid was not felt, no cervical glands Lungs and heart were negative Blood pressure 105/85 The liver and spleen were not enlarged No masses were felt in the abdomen The penis was underdeveloped, the scrotum very small and empty The testicles could not be felt in the region of the annulus inguinalis Neurological findings were negative except for fundus changes

Laboratory findings basal metabolism rate −12%, blood tests normal, blood sedimentation rate 43 mm in an hour, calcium 11 mgm %, phosphorus 1 36 mgm %, total cholesterol 200 mgm %, serology negative Blood sugar tolerance curve flat, maximum 123

X-ray findings x-ray of the skull showed a general increase of intra-cranial pressure The floor of the sella was flattened and the posterior clinoids decalcified The lower end of the left femur showed an oval-shaped area of increased radiance the size of a half dollar, cyst-like in appearance The upper end of the right fibula also had an area the size of a dime of increased radiance The entire skeleton was not decalcified The findings were suggestive of suprasellar cyst

Final diagnosis Neurofibromatosis Recklinghausen, suprasellar cyst, bone cysts in the femur and fibula, hypogonadism

Case II *E S* (No 8847), a 15-year-old female student, was referred to the Joseph H Pratt Diagnostic Hospital in April, 1942, because of leanness She had stopped eating normally about two years before entry Shortly after her change in diet her menstrual periods, which had been irregular, stopped completely and did not reappear Her weight dropped from 115 pounds to 74 pounds on admission During the weight loss she developed fatiguability and her breasts shrank She became listless and remained indoors Her teeth decayed considerably but no tooth broke spontaneously She stated that she was afraid to eat for fear of becoming too fat Her family stated that she had become very antagonistic

Physical findings The patient was a scrawny, emaciated girl with a pigmented spot beneath her right eye The hair of the scalp was normal in texture, axillary and pubic hair was absent There was also a pigmented spot on the dorsum of the fourth left finger She said that this particular spot had appeared recently On several places over the body there were café au lait spots, but no cutaneous fibroma Pupils reacted to light and accommodation The optic fundi were normal There was no adenopathy The thyroid gland could not be felt Lungs vesicular breathing, no rales The heart was small in size Pulse 72 Reflexes normal

Laboratory findings Calcium 9 6 mgm %, phosphorus 3 5 mgm %, phosphatase 2 Bodansky units Glucose tolerance test flat curve, highest hevel 124 Fasting blood sugar 75% Blood sedimentation rate 5 mm in one hour Basal metabolism rate −42% Electrocardiogram normal

X-ray examination showed an oblong rarefied area in the shaft of the lower end of the left tibia This cyst-like area did not show periosteal origin Diagnosis longitudinal bone cyst of the left tibia

Clinical diagnosis Anorexia nervosa, Recklinghausen's neurofibromatosis (forme fruste) with one bone cyst in the tibia

IV HYPERPARATHYROIDISM WITH GENERALIZED DECALCIFICATION AND FIBROCYSTIC LESIONS OF THE SKELETON, AND OSTEITIS FIBROSA CYSTICA DISSEMINATA TWO DIFFERENT CLINICAL AND PATHOGENIC ENTITIES

Hyperfunction of the Parathyroid as a Pathogenic Factor Since the successful extirpation by F Mandl in 1926 of a parathyroid adenoma in a case of Reckling-

hausen's osteitis fibrosa cystica, this term has been used in the literature as synonymous with hyperparathyroidism Here an attempt will be made to show whether or not this designation is justified

A connection of the function of the hyperparathyroid with malacic bone disease was suggested early in this century Enlargement usually of one but sometimes of more parathyroid bodies has been found in osteomalacia (Erdheim 1907, Maresch 1916, Strauch 1922, and others), in senile osteoporosis (Todyo 1912), in human rickets (Pappenheimer and Minot 1921), in multiple myeloma (Barr and Bulger 1930, Soffer and Cohen 1943), in carcinomatous metastases in the bones (Klemperer 1923, Soffer and Cohen 1943), in uremic conditions of kidney insufficiency (MacCallum 1905 and later many others), and in osteitis fibrosa cystica (Askanazy 1904, Molineus 1913, Harbitz 1915, Schlangenhauser 1915, Maresch 1916, Meyer 1917, Sauer 1922, Hartwich 1922, Dawson and Struthers 1923, Stenholm 1924, and Hoffheinz 1925)

Erdheim believed the enlargement of the parathyroid to be a reactive hypertrophy secondary to any kind of bone disease with demineralization This opinion, based on the observations in cases of osteomalacia, was shared more or less by the other authors describing enlargement of the parathyroids in bone diseases up to 1926 In that year Mandl extirpated an adenomatous parathyroid body in a case of osteitis fibrosa cystica, with the result that the patient's negative calcium balance disappeared, he gained weight and was able to walk After operation, the bones showed increased density, but the deformation of the skeleton and cyst-like structures of the bones persisted Later the patient again became worse, was bedridden, and died in 1933, after a second operation in which two parathyroids were removed At autopsy no parathyroid tissue could be found

McCallum and Voegtlin (1909), Hanson (1924), Collip (1925), and Greenwald and Gross (1926), studying the physiology of the parathyroids, found that the parathyroid bodies regulate the calcium metabolism Extirpation of one or more of these glands results in a low level of the serum calcium in serum and lowers the level of serum phosphorus (Robinson, Huffmann, and Burt 1927) Injection of parathyroid hormone (Collip) simultaneously produces increased excretion of calcium and phosphates in the urine, causing negative calcium balance (Greenwald and Gross) In experimental hyperparathyroidism, in addition to these metabolic changes, the trabecular system of the entire skeleton as well as cortical parts are partly decalcified and replaced by fibrous tissue (Jaffe, Bodansky, and Blair) The stroma of the fibrous tissue does not show any particular structure, but extensive osteoclastic activity is demonstrated by the presence of conglomerations of osteoclasts (Thomson and Collip, Turnbull, Jaffe) Different opinions explaining the mechanism of parathyroid action upon the calcium metabolism do not agree (Albright and coworkers, Neufeld and Collip), but it may at least be said with certainty that wherever in experimental hyperparathyroidism resorption of bony substances is observed, osteoclasts appear in great numbers Osteoclastic activity therefore seems to be connected with parathyroid activity, even if we do not know the detailed mechanism of it A high level of serum calcium and depression of the level of serum phosphorus, together with negative

calcium balances with increased urine-calcium output, are the metabolic symptoms of hyperparathyroidism The histologic feature is an increased number of osteoclasts In addition to these basic features caused experimentally with toxic doses of parathyroid extract, deposition of calcium in other organs, especially in the kidneys, lungs, and gastrointestinal tract, may occur (Huepei, Jaffe, and coworkers) Since discovery of the physiology of parathyroid function, hypercalcemia and negative calcium balance have been searched for in cases where hyperfunction of the parathyroid was suspected Indeed, chemical analysis of the serum for calcium and phosphorus and phosphatase activity, and calcium balance studies are now considered the prerequisite for the clinical diagnosis of hyperparathyroidism

The histology of the hypertrophic or adenomatous parathyroid gland has been described by different authors, but most extensively by Castleman and Mallory

In surveying the cases of hyperparathyroidism (hyperplasia or adenoma) reported in the literature with different grades of demineralization of the skeleton and fibrosis, two theories are found (1) that only those fibrocystic bone changes which display simultaneously high serum calcium and evidence of negative calcium balance are a result of hyperparathyroidism, and (2) the theory that hyperparathyroidism is the only etiological factor in osteitis fibrosa cystica Recklinghausen As recently as 1943, I Snapper wrote in his book, "Medical Clinics on Bone Diseases," that "The original name of 'generalized fibrocystic osteitis' which was given by Recklinghausen himself is therefore not altogether correct As a hyperfunctioning parathyroid adenoma is always present, according to present knowledge, the name hyperparathyroidism is more appropriate"

The first of the above two theories, that high serum calcium and negative calcium balance are the symptoms of hyperfunction of one or more parathyroid bodies, has proved in all cases to be in conformity with the operative or post-mortem findings After extirpation of one hypertrophic parathyroid body, the serum calcium as well as the calcium balance become normal The fibrocystic bone changes, however, do not disappear in all cases

The second theory, however, that hyperparathyroidism is found in all cases of osteitis fibrosa cystica Recklinghausen and is considered to be "the" etiology of this condition, does not conform with the facts observed in clinical and in post-mortem examinations Approximately 50 per cent of the cases diagnosed as osteitis fibrosa cystica display normal serum calcium and normal calcium balance, and no histological signs (agglomeration of osteoclasts) are found (F Albright and coworkers, Falconer and Cope) On operation of such cases, the parathyroids are not found to be enlarged

This discrepancy of the presence and absence of symptoms of hyperparathyroidism in apparently the same disease, osteitis fibrosa cystica Recklinghausen, certainly does not prove that "every case of Recklinghausen's disease depends on hyperparathyroidism" There are two possible explanations of the apparent discrepancy: (1) It may be that we are dealing with two etiologically different diseases, one due to some unknown cause, the other due to primary hyperparathyroidism (2) Or it may be but one disease, of unknown origin, which may or

may not be associated with hyperparathyroidism The first idea, that two etiologically different diseases are hidden under the commonly used designation "generalized osteitis fibrosa cystica," is expressed by Albright and coworkers These authors suggest the term "osteitis fibrosa cystica disseminata" for a clinical entity of unknown origin which is characterized by disseminated spotty involvement of the skeleton, normal serum calcium values, normal calcium balances, and pigmented areas of the skin The designation "osteitis fibrosa cystica generalisata" should be reserved for a hormonal disorder occurring in hyperparathyroidism with high serum calcium, negative calcium balance, and with fibrocystic bone involvement They correctly postulate that any disease due to hypersecretion of the parathyroid hormone is bound to affect the entire skeleton, as noted in experimental hyperparathyroidism

The second possibility, that we are dealing with but one disease which may or may not be associated with hyperparathyroidism, eliminates itself if we analyze the clinical symptoms and clinical course of these various patients exhibiting increased and normal serum calcium values and negative and normal calcium balances with fibrocystic bone changes It will then be evident that two different clinical entities, both displaying fibrocystic bone manifestations, exist, and that they are readily distinguishable not only by their serum calcium levels and calcium balances but even by their outward appearance, their clinical symptoms, and by the course of the disease

Symptomatology of Hyperparathyroidism with General Decalcification and Fibrocystic Bone Lesions Patients with this disease are usually over 30, most frequently over 40 years old *Pain* is usually the first symptom The bone pain is localized at first and later spreads all over the skeleton Deformities of the skeleton occur relatively late in the course of the disease Shortening of the whole body develops, because of kyphosis and bowing of the legs The chest becomes barrel-shaped Grotesque deformities of the limbs rarely occur in the first stages Spontaneous fractures may happen after trauma The occipital part of the skull is not deformed and protruding X-ray pictures of the skeleton show generalized decalcification and also some areas of cystic involvement, but rarely grotesque disfiguration The skin is never involved Areas of abnormal pigmentation are not observed The muscles are flabby and weak Electric irritability is decreased In the course of the disease progressive general weakness is the outstanding symptom, and the patient becomes bedridden Sometimes polyuria and urinary symptoms are early complaints Calcium phosphate stones and calcification of the kidney tissue are found in many cases The occurrence of calcium phosphate stones of the kidney may be observed even earlier than the bone pains as an initial symptom of hyperparathyroidism Metastatic calcification has also been reported to occur relatively early in the course of the disease Renal insufficiency develops in the last stages and is frequently the cause of death, or the patients die in a condition of general marasmus Chemical features include high serum calcium, low or normal serum phosphorus, and high phosphatase (usually above 10 Bodansky units) This definite clinical entity is revealed by patients described under various headings by Mandl, Gold, Har-

mon, Shorr, McClellen, and Dubois, Bauer, Albright, and Aub, Barr and Bulger, Cases 1, 2, 3, Wilder, Snapper, Hunter and Turnbull, Ettinger and Magendantz, Albright, Sulkowitch, and Bloomberg, Compere

Those cases of primary hyperparathyroidism and generalized decalcification of the skeleton with metastatic calcification of the kidney tissue which end in uremia should be distinguished from cases where primary kidney insufficiency produces reactive hyperfunction and enlargement of the parathyroids resulting in high serum calcium levels but simultaneously displaying high serum phosphorus values (McCallum and Voegtlin, Ballin and Gershwin, Elsom, Wood, and Ravdin, Curtis and Feller) In similar cases Albright, Drake, and Sulkowitch describe fibrocystic bone changes and metastatic calcification, especially involving the tissue around the joints and producing Monckeberg's type of arteriosclerosis

Symptomatology of Osteitis Fibrosa Cystica Localisata and Disseminata In contrast to the changes found in hyperparathyroidism, here the bone involvement starts in early life, mainly in the first two decades The first symptom is not pain, but deformity, which later develops into grotesque curvatures, especially of the limbs but also of the spine The femora exhibit a characteristic lateral curvature starting at the hip and displaying the shape of a boomerang ("shepherd's crook") The tibia and fibula and the upper extremities, especially any of the fingers, may also be disfigured, but not to such a degree as the femur Frequently the occipital part of the skull has a cap-like deformity due to an expansion by the fibrocystic involvement In many cases an epulis-like deformity of the jaw has been described X-ray examination shows the involved bone to be grossly disfigured The shafts of the long bones are expanded, the corticalis is thinned out and often overgrown by fibrocystic masses The same fibrocystic lesions are disseminated over the skeleton, but a great part of the skeleton has normal structure and is not decalcified The skull in the x-ray picture reveals, besides the cystic involvement, many areas of hyperostotic densities like leontiasis osseum

Spontaneous pain is not an early symptom For this reason, the patients are able to work, even to exercise Pain occurs after trauma In the more advanced cases spontaneous fractures are frequently observed, they may even be the cause of discovery of the disease by the consulted physician Café au lait spots or brown pigmented areas of the skin are present in most of the cases, observed on the site of the areas of bone involvement In rare instances fibromas of the skin are also described, occurring simultaneously with the brown spots Flabbiness of the muscles and abnormal mobility of the joints or diminished electrical irritability are not present Metastatic calcifications do not occur The course of the disease is rather slow The patients do not display symptoms of general cachexia and weakness or of renal failure Death occurs as a result of intercurrent diseases The chemical features are normal serum calcium, normal serum phosphorus, and slightly increased phosphatase Patients exhibiting the symptomatology of osteitis fibrosa cystica disseminata and localisata are described under various headings by von Recklinghausen, Cases 5 and 6, Loetsch,

Morton, Young and Cooperman, Beadfield, Hunter and Turnbull, page 269, Freund and Meffert, McCune, Albright, Butler, Hampton, and Smith, Coleman, Lange, Falconer and Cope

The great difference between the outward appearance of patients suffering from hyperparathyroidism with generalized decalcification and fibrocystic lesions of the skeleton on one hand and osteitis fibrosa cystica disseminata on the other is most impressively demonstrated by comparison of the classical photographs published by Harmon, Shorr, McClellan, and Dubois (page 217) with Morton (page 535) or the skeleton of Recklinghausen's original Case 6 with Jaffe's photograph of a cadaver of a patient with hyperparathyroidism

These differences of the clinical symptomatology demonstrate as clearly as the differences in the chemical findings of calcium metabolism that the pathogenesis of osteitis fibrosa cystica Recklinghausen is not uniform Different pathogenic principles are apparently able to produce fibrocystic bone changes similar in their gross appearance but distinguishable by their clinical development and by their features of calcium metabolism For one group of fibrocystic bone lesions, its pathogenesis as a result of hyperparathyroidism is evident For this reason, the designation of this clinical entity as "hyperparathyroidism with generalized decalcification and fibrocystic lesions of the skeleton" seems more appropriate than "osteitis fibrosa cystica generalisata" (Albright and coworkers) The term "osteitis fibrosa cystica" should be reserved for the group designated by Albright and coworkers as osteitis fibrosa cystica localisata and disseminata (mono-ostotic and polyostotic fibrous dysplasia of the bones (Lichtenstein and Jaffe)), since the skeletal lesions of this group are the main feature of the disturbance

Histology of Osteitis Fibrosa Cystica Localisata and Disseminata (Recklinghausen) According to Recklinghausen, Morton, Hunter and Turnbull, Freund and Meffert, Lichtenstein and Jaffe, and many others, the localized as well as the disseminated type of osteitis fibrosa cystica exhibit the same histological features In their important study entitled "Fibrous Dysplasia of Bone," Lichtenstein and Jaffe investigated the histology of the disease The following discussion is based on their study, for it is the most detailed histological analysis that has been published on the subject

Fibrous Tissue These authors reported that "The interior of a given bone, wherever it is affected, is occupied by fibrous connective tissue, often varying from place to place in its detailed histological composition Specifically, apart from the osseous and the cartilagenous elements, the connective tissue in some places or throughout, may be rather cellular, composed of immature, small spindle cells in rather loose and whorled arrangement On the other hand, in some places or throughout, the connective tissue may be rather poorly cellular and highly collagenous Furthermore, in some areas it may appear edematous or myxomatous, or even show some cystic softening Altogether it would seem that the spindly and rather whorled connective tissue and that the collagenous, edematous, or myxomatous areas represent modifications of this basic tissue "

"Though the connective tissue on the whole tends to be relatively avascular,

one sometimes encounters sporadic fields dominated by enlarged and also engorged, thin-walled blood channels Surrounding them, one may also observe blood extravasations The presence of hemosiderin pigment in such areas points to previous capillary hemorrhages which have been reabsorbed "

Nests of multinuclear giant cells may be related to resorption of blood extravasation *Mallory pointed out many analogous instances of the attraction of* endothelial cells into a fibrous but cellular tissue which arises as a result of retrograde processes (foreign body giant cells) Mallory and also Barrie claim that the presence of such giant cells in a tumor involving bone signifies only erosion or disintegration of bone substance Hemorrhages may occur in the fibrous and granulation tissue, which increases the number of foreign body giant cells Cyst formation in the fibrous tissue may result from the retraction, collagenization, and softening of the fibrous connective tissue as well as from absorption of bleeding in such tissue Certainly the cyst formation is the secondary and not the primary process of the disease

Osseous Tissue The present writer does not believe that a metabolic or a genetic unbalance of ana- and katabolism of the osseous tissue in the primary disturbance in osteitis fibrosa cystica disseminata The new growth of fibrous tissue in bones results rather in the replacement and in secondary slow new formation of osseous tissue

Lichtenstein and Jaffe describe the histological changes in the osseous tissue as follows "The connective tissue in the affected area is likely to present trabeculae of bone formed through metaplasia One finds little evidence of osteoclastic resorption of such trabeculae, and whatever reconstruction they undergo seems to proceed very slowly Trabeculae of metaplastic fiber bone are of variable size and contour They are irregularly dispersed within the fibrous tissue, not following any regular pattern, and their number and location seems to be determined by the random distribution of the blood vessels in their immediate vicinity "

"Small islands of hyaline cartilage may be found embedded in the connective tissue in an occasional fibrous dysplastic lesion, and apparently these islands, too, result from metaplasia In some instances, however, they are larger and more numerous and may even constitute a striking feature of the lesion "

The only point of difference to be found with Lichtenstein and Jaffe's very complete description of the fibrotic growth in the osseous lesion is the question whether their opinion is correct that the occurrence of such a hyaline cartilage within the fibrotic growth is an integral part of the disease and not merely fortuitous, since we also encounter such islands of hyaline cartilage in inflammatory osteomyelitic processes

Their description agrees in its main points with the histological analysis of A H T. Robb-Smith Smith found that the cortical zone is much narrower than that found in normal bone, but within itself shows no abnormality In the severe cases, the cortical bone is thinned out and may be replaced by fibrous tissue All observers agree that the changes in the bones are essentially a replacement of the fatty or cellular marrow by fibrous tissue with an alteration of the bone

architecture New bone is formed of fibre bone by apposition Evidence of new bone formation is seen in the presence of a broad layer of osteoblasts beyond the osteoid bone There is only a moderate amount of osteoclastic resorption, and no collections of osteoclasts are present

Just the opposite is the case in the histological picture of hyperparathyroidism with generalized decalcification and fibrocystic involvement of the entire skeleton Here the osteoclasts are prevalent Turnbull speaks of the appearance of "osteoclastomas" Thomson and Collip express the opinion that the most acceptable theory of the action of the parathyroid is that it stimulates the osteoclastic process

Histologic Comparison of Osteitis Fibrosa Cystica Disseminata (Recklinghausen) with Hyperparathyroidism with Generalized Decalcification and Fibrocystic Lesions of the Bones At this point a comparison of the histology of osteitis fibrosa cystica disseminata with the histological features produced in osseous tissue by hyperparathyroidism may be indicated to demonstrate the difference of the histological pattern in both diseases

The first to describe the histological features of hyperparathyroidism were Dawson and Struthers, although these authors did not connect the adenoma found at autopsy in their case with the etiology of the case described under the title "Generalized Osteitis Fibrosa" (1922) Turnbull (1931) published the classical description of the histological pattern of bones obtained from biopsy material of cases where adenomatous parathyroid bodies actually were removed by operation

A hormonal disturbance as initiated by the hyperfunction of the parathyroids or by injection of massive doses of parathyroid hormone results in a general metabolic disorder, which is bound to involve the entire skeleton In contrast, osteitis fibrosa cystica localisata and disseminata, as already indicated by the name, alters not all parts of the osseous system, but manifests itself in spotty lesions or in irregular larger areas scattered about the skeleton The outstanding phenomenon of hyperparathyroidism produced by hyperactivity of the gland and by injection of the hormone (Jaffe and Bodansky, Turnbull, Johnson, Abeloff and Sobel, Rutishauser) is the lacunar resorption of osseous substance resulting in secondary replacement with fibrous tissue In osteitis fibrosa cystica disseminata, however, the fibrous growth is the primary and dominating feature The trabecular structures are replaced only in the areas involved The resorption of osseous substance in osteitis fibrosa cystica disseminata is neither lacunar nor is it a generalized process Demineralization is not found in the areas where the fibrous growth displaces and replaces the bony structures In hyperparathyroidism we find subperiosteal decalcification with subperiosteal replacement of the outer layer of the corticalis by fibrous tissue In osteitis fibrosa cystica disseminata the subperiosteal outer layers of the corticalis are not involved (Falconer and Cope, Fig 24) The cortex is thinned from the inside, the thinned cortex becomes deformed and is sometimes entirely outgrown by the fibrous growth (Lichtenstein and Jaffe, Fig 2, page 778)

In hyperparathyroidism, numerous osteoclasts, conglomerated or in layers

upon the osteoid zones, or osteoclastoma, i e nests of osteoclasts (Turnbull), are found Osteoblasts are also numerous, but the osteoclasts characteristically prevail Just the opposite is the case in osteitis fibrosa cystica disseminata Here osteoclasts are found only in small numbers, often no osteoclastic activity at all being present, while osteoblasts are found in normal amounts (Robb-Smith, Albright, Butler, Hampton and Smith, Farber, Bennet) The finding of collections of osteoclasts in hyperparathyroidism is the most characteristic feature, enabling us to distinguish histologically the two conditions under discussion

Hyperostotic phenomena are not present in clinical hyperparathyroidism In osteitis fibrosa cystica disseminata, in cases where the skull is extensively involved, areas of hyperostosis (osteosclerosis) are found, sometimes simulating leontiasis ossium, interchanged with areas of fibrocystic involvement (Morton, our own case V)

In regard to the fibrous tissue, it must be realized that fibrosis in hyperparathyroidism is the result of a metabolic disorder in which calcium is resorbed from osseous tissue, subsequently being replaced by connective tissue In osteitis fibrosa cystica disseminata, the fibrous growth is the primary cause of the replacement of the trabecular structure of the osseous tissue and of the narrow spaces The fibromatous growth, especially in the localized form of osteitis fibrosa cystica, behaves not unlike plasmacytoma in multiple myeloma, or xanthoma in osseous xanthomatosis, or Ewing's sarcoma, replacing osseous tissue and bone marrow without any osteoclastic activity In the disseminated form of osteitis fibrosa cystica the replacement of osseous tissue by fibromatous growth follows the same pattern but is more extensive and wide-spread The characteristic feature, however, of this analogous reaction of the osseous tissue to foreign tissue elements is that the replacement of osseous tissue is not brought about by osteoclastic resorption, but by rarefication of the original osseous structures as a result and secondary to the ingrowth of another kind of tissue in the osseous matter

The structure of the fibrous tissue in hyperparathyroidism is that of uniform connective tissue Collagen and fibrocytes with narrow spindle nuclei are usually not too common (Turnbull) In osteitis fibrosa cystica localisata and disseminata, collagen and spindle cells are predominant The fibromatous tissue in areas in which the fibrous masses are not too gritty and rubbery, and as a consequence poor in cells, shows a definite pattern such as palisade-like structures and whorls of numerous small spindle cells The significance of the whorled arrangement of spindle cells as regards the etiology of the fibromatous growth in osteitis fibrosa disseminata in relation to the genesis of neurofibromatosis has already been discussed in the paragraph describing the histology of this disease

Cyst formation, together with occasional bleeding in the cysts and in the fibrous tissue, may occur in hyperparathyroidism as well as in osteitis cystica disseminata It is not possible to distinguish these diseases by the presence or absence of cysts because the phenomenon is common to both conditions The cysts may originate in the vulnerability of the fibrous tissue to strain or to exogenous trauma

Analysis of von Recklinghausen's Original Cases At this point it will be of interest to analyze the original cases of "fibroeser Ostitis" of Recklinghausen and to determine whether the described patients were cases of osteitis fibrosa cystica disseminata or cases of hyperparathyroidism with generalized decalcification and fibrocystic lesions of the skeleton

In Recklinghausen's original article, "Die fibroese oder deformierende Ostitis, Osteomalacie und osteoplastische Carcinose," we find sixteen cases described four cases probably of Paget's disease, five cases of osteomalacia, four of osteoplastic carcinomatosis, and three of a disease which he reported as "osteitis fibrosa with fibrous tumor and cyst formation " These latter three cases, numbered 5, 6, and 7, are considered to represent the clinical and anatomical features of Recklinghausen's bone disease In Case 6 the total skeleton, famous since then, is pictured The patient died in 1846, and the skeleton was given to the collection of the pathological institute of Strassburg, where Recklinghausen later found it He says that "the deformities of the bones are on the same areas and of the same proportions as those in Case 5 The similarity of the deformities in these two cases is so great that I am justified in assuming that the findings inside of the bones are also analogous " In fact, Cases 5 and 6 show the outstanding characteristics of the disease later designated as "osteitis fibrosa cystica disseminata " The basilar part of the occipital bone is cap-like, distended, and "almost rectangular, curved to the ascending part of this bone " Almost all the bones show areas of tumor-like expansion In both cases the femur exhibits the characteristic shape of a shepherd's crook (boomerang), and the upper part of the shaft is three times as large as normal

The clinical history of Case 5 reveals only that this 65-year-old woman died of pneumonia The bone deformities had apparently been present for a long time, and they were not the reason for hospitalization The clinical history of Case 6, a 40-year-old woman, is not known Her skeleton is the classical example of the bone changes described later as osteitis fibrosa cystica disseminata

Case 7 does not show the grotesque deformities of the bones or the tumor-like expansion of the shafts of the femora found in Cases 5 and 6, as may be seen on comparison of the excellent colored drawings in the original article (Table I, Figure 2, and Table III, Figure 8) Instead, the femur in Case 7 is "curved irregularly, shortened, and flexible " "One could artificially bring about severe disfiguration of the bones by distortion of the limbs of the corpse " (Compare the photograph of the cadaver of a woman with hyperparathyroidism in Jaffe's paper) Tumor-like expansion of the shaft, as in Cases 5 and 6, is not present in Case 7, but the diaphyses are slightly thickened and expansion of the cortex, if present at all, involves only a localized small area (Table II, Figure 7, Fibula) The clinical history is altogether different from that of Case 5 The disease developed when the patient was forty and revealed itself by spontaneous fractures and development of intense pain in many bones The patient lost weight rapidly and could not move his leg because of pain He died from cachexia one and a half years after the onset of the disease

Jung, who reinvestigated (1933) the original autopsy reports of Recklinghausen

in the files of the pathological institute of Strassburg, found the following statement on Case 7 "Above the left thyroid gland, a lymph gland, red-brown in color is present" Jung raises the question whether this lymph gland might not have been a parathyroid adenoma According to the case history as well as the findings discussed above, Jung may well be right in this assumption In addition to the protocol of Case 7 in the original publication (1891), Jung found the protocol of an autopsy by Recklinghausen in 1901 of a case of "osteitis of the fibrocystic type" On this case Recklinghausen's statement reads, "At the right side of the inferior pole of the thyroid lobe a cystic tumor the size of a nut, 4 x 3 cm, is found The tumor can be easily separated from the thyroid and has a soft white capsule The tumor consists of a grayish-white tissue which contains cystic spaces filled with seromucous fluid" The femur of this case, also pictured, shows pliability like that of fibrous tissue (Jung, Figure 7, p 203), but no tumor-like fibrous overgrowth expanding the shafts as seen in Cases 5 or 6 of Recklinghausen's original paper The clinical history of this case (1901) is reported with its anatomical findings by Recklinghausen in this book "Untersuchungen ueber Rachitis und Osteomalacie," (1910, p 340) It is the history of a woman (Frau Michel), 33 years of age, with characteristic symptoms and the deathly course of hyperparathyroidism with generalized decalcification and fibrocystic bone changes It is indeed possible that Case 7 of the original paper, and it is evident that the case autopsied ten years after the original Recklinghausen publication, both represent primary hyperparathyroidism with generalized decalcification and cystic bone lesions One is, however, not justified in assuming that hyperparathyroidism was present in Cases 5 and 6, which are the first original cases Recklinghausen published as osteitis fibrosa cystica

In the chapter on "Recklinghausen's Disease Hyperparathyroidism," by Snapper, one may be led into such an assumption Snapper writes on page 9 that "Jung has been able to consult the original autopsy reports, which von Recklinghausen wrote himself in Strassburg after the autopsy on his first patients with generalized fibrocystic osteitis In these protocols the following passage is found" There follows the report of Case 7 (1891), where Recklinghausen mentions the presence of a reddish-brown lymph gland below the thyroid, and the report of the second autopsy, where a cystic tumor attached to the thyroid was present In the report of Snapper of the "second autopsy" it is not mentioned that this was performed not on the patient reported in his first publication, but on a case which came to autopsy ten years later Even if the reinvestigation of Jung holds true as regards the suggestion of hyperparathyroidism in Case 7 and the other case in 1901, these are not "Recklinghausen's first patients with generalized fibrocystic osteitis" On the contrary, the name fibrous osteitis with cyst formation was first described (1891) in Cases 5 and 6, which were probably not cases of hyperparathyroidism but of "osteitis fibrosa cystica disseminata" F Albright also expressed this opinion in a discussion of Kornblum's paper The quotation of Jung by Snapper may give the wrong impression, that the first patients described by Recklinghausen were "posthumously" indicated by Jung to have hyperparathyroid tumors, thus justifying Snapper's assumption as

expressed on page 33 that "Every case of Recklinghausen's disease depends on hyperparathyroidism"

There is no reason to attach Recklinghausen's name to the clinical and genetic entity of "hyperparathyroidism with general decalcification and fibrocystic bone lesions," but there is good evidence, based on the pictures and the anatomical findings on Cases 5 and 6 of his original publication, for connecting his name with the entity "osteitis fibrosa cystica localisata and disseminata"

Osteitis Fibrosa Cystica Disseminata with Secondary Reactive Hyperplasia of the Parathyroids It must be stated that in severe cases of osteitis fibrosa cystica disseminata, fluctuating calcium values observed in different time intervals (slightly elevated interchanging with normal serum calcium) are occasionally found (Priesel and Wagner, Pagniez, Plichet, and Fauvet, Lange) This may be interpreted as a secondary reactive hyperfunction of the parathyroid as it may occur in any type of malacic bone involvement such as osteomalacia, osteoporosis, myeloma, or metastatic carcinomatosis of the skeleton (Erdheim, Soffer and Cohen, Klemperer) Such occasional existence of slight elevation of srum calcium cannot be taken alone without other clinical evidence as proof of the presence of primary hyperparathyroidism

Berblinger (1937) and Snapper (1943) reported cases, which probably belong to this group of osteitis fibrosa cystica disseminata with secondary reactive hyperplasia of the parathyroids Berblinger's case, designated as "generalized osteitis fibrosa Recklinghausen," exhibited severe bone deformities during her whole life At the age of 31, she was erroneously operated for a so-called sarcoma of the upper maxillary bone (tumor of the epulis type) She lived to the age of 64, when a perforated appendix terminated her life The published photographs of her skeleton demonstrate the characteristic bone deformities of osteitis fibrosa cystica disseminata At autopsy two slightly enlarged parathyroids were found, but no generalized decalcification of the skeleton was present

The patient reported by Snapper in his book, "Bone Diseases" (p 56), under the heading "Parathyroid adenoma in a patient, 24 years of age, with recurrent osteofibromas of the skull without other bone manifestations," suffered also from an epulis-like tumor of the lower jaw (revealed by x-ray as a cystic tumor of the mandibula) No generalized decalcification of the skeleton was found Later, an additional tumor of the left superior maxillary bone developed Exophthalmos of the left eye was present The serum calcium was upper border normal (11 2–11 6), with normal serum phosphorus (3 0–3 75 gm), normal phosphatase, but increased calcium secretion in the urine (150–385 mgm) instead of normal (100–150 mgm) No mention is made of any kind of pigmentation of the skin or mucous membranes of the mouth A resection of the entire upper maxillary bone was performed Histological examination revealed many strains of fusiform tissue cells The fibrous tissue often surrounded masses of osteoid tissue Only a few giant cells were present, which, however, were always in contact with bone or osteoid tissue The most probable diagnosis was osteofibroma At a second operation, an enlargement of one parathyroid was found (1 x 0 5 cm)

Neither the clinical history and symptoms (bone pain, weakness and immobility, progressive course, high serum calcium) nor the gross anatomical manifestations (generalized decalcification), nor the histological findings (conglomeration of osteoclasts) characteristic of primary hyperparathyroidism were present, but both cases exhibited the features considered as typical for osteitis fibrosa cystica (gross disfiguration of bones without spontaneous pain and without incapacity to work, slow course not terminating in death from the disease) For this reason, one is not justified in assuming that the moderate hyperplasia of the parathyroids of these patients was the primary disturbance causing the disease It seems more likely that a secondary reactive hyperplasia of the parathyroids may have developed in these rare cases of osteitis fibrosa cystica disseminata without causing permanent or progressive symptoms of hyperparathyroidism Analogous observations of secondary reactive hyperplasia of the parathyroids are reported in other malacic bone diseases (osteomalacia, myeloma, metastatic carcinosis of the bones)

Summary 1 The development of our knowledge of hyperparathyroidism and its evaluation as a pathogenic principle are discussed

2 It is demonstrated that the outward appearance, the clinical features, the clinical course, and the cause of death in hyperparathyroidism with generalized decalcification and fibrocystic lesions of the skeleton are entirely different from corresponding features in osteitis fibrosa cystica localisata and disseminata Both diseases are heterogenous clinical entities

3 Recklinghausen's original cases are analyzed The first two, described as fibrous osteitis (Cases 5 and 6), exhibit the features of osteitis fibrosa cystica disseminata Therefore, the name of Recklinghausen should be connected with osteitis fibrosa cystica disseminata and not with primary hyperparathyroidism

4 Analogous to observations on cases with diffuse malacic bone disease, secondary reactive hyperplasia of the parathyroids may also occur in rare instances in osteitis fibrosa cystica disseminata, but without the progressive generalized symptoms of primary hyperparathyroidism

Case of Hyperparathyroidism with Generalized Decalcification and Fibrocystic Lesions of the Bones *Case III* (previously reported by Ettinger and Magendantz) *J C* (No 807), a 30-year-old male, was admitted to the ward of the Boston Dispensary (unit of the New England Medical Center) in March 1933 For the past year and a half he had noticed pain in both legs which came on when he walked, when he was in bed there apparently was no pain, and only a little when on his feet during the day He had lost weight during the past two years, from 140 pounds to admission weight of 107 pounds He gradually had become so weak with the pain in his legs that he was unable to do any work He tired very easily, especially during the previous few months He had given up his heavy work as a carpenter a year before hospital entry He never had fever or cough On questioning it was learned that he had had slight polyuria and polydipsia in 1931. Since that time he had had to get up several times during the night A few weeks before admission he stated he had had to urinate every three hours during the night He had never noticed blood or pus in the urine

Physical Examination The general impression was that of a pale, emaciated, sick-looking man There was no edema No deformities were noted on the legs, skull, or chest The bones, however, were painful on pressure The fundi were normal The tongue was not remarkable Neck an indefinite pin-sized mass was palpable along the medial inferior aspect of the left lobe of the thyroid Lungs vesicular breathing, no rales Heart normal in size, slight murmur at the apex Blood pressure 115/80 The liver and spleen were not palpable Skeleton no signs of fracture, no exostoses, no clubbed fingers, tenderness of all long bones to touch Reflexes normal There was no remarkable muscular hypotonia

Laboratory Findings Histamine refractive achlorhydria of the stomach Many leukocytes in the fasting contents Stool specimen negative for blood Basal metabolism rate -6 3, hemoglobin 60%, white-cell count 6,100, erythrocytes 3 2% Non-protein nitrogen 44 7 mgm %, calcium 16 9%, phosphorus 3 0 mgm %, blood urea 18 1 mgm %, sodium chloride 492 mgm % Urine clear, light yellow, slightly acid, specific gravity 1 010, albumin slight trace, no Bence-Jones, many leukocytes, a few red blood casts and hyaline casts The dilution and concentration test of the kidney revealed isostenuria

X-ray Findings The pelvis and lumbar spine showed extensive osteoporosis with areas suggestive of beginning cyst formation The skull showed a mottled appearance due to small areas of decreased and increased density The calcium content of the skull seemed markedly decreased Apparently the lower jaw and all the bones of the face were involved in a decalcifying process The rest of the long bones showed the same findings in varying degrees The kidneys showed innumerable areas of increased density, each about the size of a millet seed lying in wedge-shaped forms, conforming to the outlines of the kidney pyramids There was no evidence of calcification in the lungs

Diagnosis Hyperparathyroidism with general decalcification of the skeleton and cystic lesions of the skeleton Extensive calcification of the parenchyma of the kidneys

The patient was transferred to the Massachusetts General Hospital At operation, Dr Churchill removed a bean-sized parathyroid adenoma from the left side of the neck The patient made a good recovery at first, but later died in a state of general marasmus Autopsy findings will be reported by F Albright

Cases Illustrating Osteitis Fibrosa Cystica Disseminata (Recklinghausen)

Case IV G P (No 11-334), a 46-year-old farmer entered the Joseph H Pratt Diagnostic Hospital in September, 1913, because of deformities of his lower limbs

Past History At the age of six the deformities of both femora were first noticed when he fractured his right femur falling over a step At twelve he injured his right femur again and was laid up with this for seven weeks He did not know whether there was a definite fracture because no x-ray pictures were taken At sixteen, he tripped on a railroad track and fractured the right femur again He was in bed for eight weeks and was put in a splint At eighteen his right thigh became swollen for no apparent reason At nineteen he was taken to a hospital where x-ray examination was done and "a strange bone condition"

was found He stated that the physicians did not know very much about the nature of this condition A piece of bone was taken from the femur at the age of 22 and his thigh was put in a splint In 1936, while stepping over an obstacle approximately one foot high, he fractured his right femur again He fractured his right forearm in 1941 Despite this continuous story of fractures and the severe deformities of his legs, he did his heavy work as a farmer There had been no spontaneous pain except on the places where he fractured his bones There had been no difficulty in urination, no polydipsia or polyuria He reported that in 1919 he passed a few stones, but none had been passed since

Physical Examination The patient gave the impression of a healthy man He had no complaints at the time of examination Both of his legs were grotesquely deformed, the right one especially had the shape of a boomerang (shepherd's crook) The tibia on the right seemed to be thickened and grotesquely deformed The upper extremities and the skull did not show any visible deformities Skin there was a small café au lait spot in the middle of the sacrum, the size of a small plum There was also a small café au lait spot on the upper right arm There were no fibromatous nodules on the skin and no abnormalities of the skin Head the frontal appearance seemed to be normal, but the transverse region of the occipital bone seemed to be bent upwards Eyes normal reaction to light and on accommodation, fundi normal, no choking Ears hearing good Mouth no pigmentation of the mucous membranes Neck thyroid not enlarged, no masses palpable Chest somewhat deformed, vesicular breathing, no rales Heart normal in size, no definite murmur heard Reflexes were normal

Laboratory findings Urine specific gravity 1 023, a few red blood cells Blood chemistry calcium 11 3 mgm %, phosphorus 3 0 mgm %, phosphatase, 7 4 Bodansky units Blood sedimentation rate 13 mm in one hour

X-Ray Findings The pelvis and femora showed a fantastic change of bony structure The os ilii showed tremendous areas of cystic-appearing bone The femora were extremely deformed, showing marked changes of the angle of the neck of the femur with the head of the femur The femur was thickened to about double its original width, markedly crooked, and also showed numerous areas of increased radiance giving the appearance of cysts Along the medial margins, apparently where stress and strain had required architectural changes, marked bony sclerosing had taken place In addition, there were a few linear transparent areas visible along the shaft of the left femur which were apparently scars from osteotomies There were several areas of patchy increased density within the bone Similar changes were present in both lower legs The left humerus was free from changes, the right showed only slight changes The ribs were essentially negative The areas of bone which were not involved showed no evidence of decalcification

Diagnosis Osteitis fibrosa cystica disseminata (Recklinghausen)

Case V S W (No 10-648), a 26-year-old single girl entered the Joseph H Pratt Diagnostic Hospital in May, 1943, because of non-painful swelling of her face and difficulties in gait In 1940 she had first noted the appearance of numer-

ous flat, *black, non-painful, pigmented areas of the lower lip Similar-sized lesions, not over 5 mm in diameter but more brownish in color, were also seen on buccal mucosa and the hard and soft palate* About this time she occasionally felt a dull discomfort in her left thigh region It did not radiate down the leg, around to the buttock, or up on the abdomen or genitalia There was no swelling, redness, tenderness, or history of trauma Motion was not limited or painful, but exercise such as dancing sometimes increased the discomfort In 1941 she noticed the development of shortening and definite limitation of motion of the left leg She subsequently walked with a pronounced limp, but still enjoyed dancing In February, 1943, pain developed in a left upper molar accompanied by marked swelling of the left face She stopped working at this time and one week later sought dental aid at the Boston Dispensary, where incision and drainage of the affected area was carried out Following this she returned for periodic dressings and treatment because of a "localized osteomyelitis of the jaw" A more extensive operation of her jaw was advised, but she refused to have this carried out She thought that the mass on her jaw had become smaller The pain ceased in the course of time and did not bother her There were no associated visual disturbances There was no general change of color of the skin and no family history of similar disease was known Her periods had been regular since the age of thirteen There were some complaints of painful menstruation on the first day, but no irregularity She is at present (October, 1943) at work again and leads a normal life

Physical Examination There was an asymmetry of the face showing a leontine type of face with asymmetry particularly on the left side, where there seemed to be hypertrophy of the entire maxillary and frontal bones There was a slight exophthalmos of the left eye The asymmetry gave the head a deformed and and swollen appearance about the left side On the mucous membranes of the lips, hard palate, and gums were dark circumscribed pigmented spots about 1 x 1 cm in size The pigmentation was deep blackish-brown, similar to pigmentation in Addison's disease There were freckles over the shoulders, but no further pigmentation of the skin Eyes pupils reacted to light and accommodation, eye grounds were normal Nose there was no deviation of the septum, no perforations Mouth uvula was not deviated, tongue showed no atrophy, many decayed teeth and old roots left, there was a scar from the old maxilla operation Neck a small nodule of the thyroid was felt on the upper pole, this definitely belonged to the thyroid There was no generalized lymphadenopathy Chest vesicular breathing, no rales Heart normal in size, regular The liver and spleen were not enlarged The spine showed a slight kyphoscoliosis The left hip was tender to pressure and visibly deformed The left femur showed considerable lateral deviation The left leg was shorter than the right While walking the patient waddled and the deformity of the femur became more clearly visible

Laboratory Findings Urine specific gravity 1 034, amber, cloudy, acid reaction, albumin +, sugar 0, sediment showed many mucous threads and squamous cells, some calcium oxalate crystals, rare red cells, and 8–10 leukocytes

per high power field, melanin test negative, numerous bacteria Blood hemoglobin 93% (Sahli), red cell count 4,840,000, white cell count 13,000, color index 0 97, the red cells and platelets appeared normal Chemistry calcium 11 8 mgm %, phosphorus 3 2 mgm %, phosphatase 5 1 Bodansky units Cholesterol total 179 mgm %, free 43 mgm %, esters 136 mgm,% Glucose tolerance fasting 123 mgm %, half hour 171 mgm %, one hour 180 mgm %, two hours 134 mgm %, three hours 121 mgm % Basal metabolic rate +19%

X-Ray Examination Chest Both diaphragms were smooth in outline, with clear angles The lung fields were free from infiltration The heart was normal in size and shape There seemed to be some structural changes present in the coracoid process of the left scapula Abdomen No abnormality was noted in the region of the kidneys There were no calcium deposits about the kidneys Skeleton Several cyst-like bone changes were present, involving chiefly the left half of the skeleton but also some of the bones on the right side The involved bones on the right were the upper ramus of the right pubic bone and the upper part of the right femur The change consisted of actual ballooning out of some of the bony structures owing to large cystic areas which were surrounded by dense areas of bone sclerosis There was a fracture with change of the axis of the neck of the left femur resulting in marked shortening of the left leg Left-sided changes were also present in the skull, involving the bones of the vault on the left, most markedly pronounced in the region of the left antrum and the left upper jaw and left zygoma Here the bone was densely sclerosed and the wall of the antrum was so extremely ballooned out at one place that one almost had the impression of complete destruction of the lower antrum wall on the left However, on some of the films it was evident that this was probably more cystic thinning than actual destruction

Diagnosis Osteitis fibrosa cystica disseminata (Recklinghausen)

V THE PATHOGENESIS OF OSTEITIS FIBROSA CYSTICA LOCALISATA ET DISSEMINATA (RECKLINGHAUSEN)

It is the purpose of this section to demonstrate by collected evidence from the previous section and from the clinical and histological reports in the literature that the pathogenesis of osteitis fibrosa cystica localisata and disseminata is closely related to neurofibromatosis Recklinghausen and its osseous manifestations In the first part of this section the clinical observations which contribute to the assumption of a common pathogenesis of osteitis fibrosa cystica disseminata and neurofibromatosis will be reported, in the second part, attention will be called to the histological features common to both conditions

Simultaneous occurrence of nodular neurofibroma, pigmented areas (café au lait spots) and osteitis fibrosa cystica disseminata in one patient Important evidence of a relationship between the two diseases would lie in the finding of neurofibromatosis, café au lait spots, and geographical map-like brown spots occurring simultaneously with osteitis fibrosa cystica disseminata in the same patient, and on searching the literature such evidence may be found Gould describes two cases with generalized neurofibromatosis of the skin, pigmented areas, and

neurofibromatous malacic involvement of the skeleton In Gould's case 1 the femora, especially the left, are involved, the pelvis and most of the bones are severely deformed Case 4 exhibits fibromas and pigmented areas of the skin, but the bone involvement is less severe Cohen and Douady discuss "Le coexistence de deux maladies de Recklinghausen chez un sujet" Pagniez, Plichet, and Fauvet report a severe case of osteitis fibrosa cystica disseminata with café au lait spots and two molluscous fibromas Mariante and Maciel describe under the title "Doencas de Recklinghausen e metabolismo Calcico," "un cas avec relation de deux maladies de Recklinghausen (osteite fibro-quistica e neurofibromatose ")[3]

These observations of the concurrence of cutaneous neurofibromas, café au lait spots, and osteitis fibrosa cystica in one patient have not been adequately appreciated in the literature This is the more surprising since there are other cases reported in the English, American, and German literature which also exhibited the clinical syndrome of both disturbances, but which are reported under the title of neurofibromatosis with multiple osseous manifestations (Stalmann, Ashton, Merklen and Israel, Uhlmann and Grossmann)

Stalmann, who published 35 cases of neurofibromatosis with bone lesions, discusses the presence of osteitis fibrosa cystica in Cases 2, 3, 4, 23, and 27 Uhlmann and Grossmann's Case 1 has the typical epulis-like involvement of the mandible which is described in quite a few cases of osteitis fibrosa cystica disseminata (Falconer and Cope, Albright and coworkers, our case V) Merklen and Israel's case, as well as that of Ashton, exhibited multiple, very extensive foci of a fibrocystic nature in the long bones with "shepherd crooking" of the neck and head of the femur, and wide areas of fibrous cystic involvement occupying the width of the long bones from cortex to cortex, leaving very little recognizable bony trabecular structure There is, therefore, little doubt that these cases of Ashton and Merklen and Israel also belong to the group which presents the features of Recklinghausen's disease, neurofibromatosis, and osteitis fibrosa cystica This simultaneous occurrence in a number of cases of two diseases as rare as neurofibromatosis and osteitis fibrosa cystica is almost certainly not mere coincidence, but gives direct evidence of the coherence of the disturbance in question

Pigmented areas of the skin, café au lait spots, and brown blotches as evidence of cutaneous neurofibromatosis in osteitis fibrosa cystica Going one step further in evolution of the diagnostic value of the cutaneous features of neurofibromatosis, many authors agree that café au lait spots and brown geographical map-like blotches alone, without cutaneous nodules, are sufficient evidence on which to base the diagnosis of neurofibromatosis (Thibierge, Weber, Darrier, Hoeckstra, Leader and Grand) (see Section II) The authoritative French dermatologist, Darrier, writes in his textbook "The pigmentations are of such characteristic appearance that when they are the only features present, a diagnosis of the

[3] Upon reading of the original article in the Argentine Radiol J, it is found that the case described would be better designated as neurofibromatosis with bone cysts than osteitis fibrosa cystica disseminata

disease (Recklinghausen's neurofibromatosis) is justifiable" This opinion is fully supported by histological examination of the subcutaneous tissues underneath the pigmented spots, as described in the first section of Stalmann's article "Most ends of the finest skin nerves show thickening and club-like expansion" The histological characteristics of the affected nerve endings also conform with Masson's recent histological investigation concerning the pathogenesis of neurofibromatosis

If the pigmented spots are thus accepted as signs and as definite evidence of the presence of cutaneous neurofibromatosis, their appearance in almost every case of osteitis fibrosa cystica disseminata reported in the newer literature (F Albright and coworkers report five new and nine old cases from the literature, Falconer and Cope two new and 27 cases already published in the literature) is of greatest significance in connecting the pathogenesis of the two diseases

The reason for omission of mention of the brown spots in the early literature concerning osteitis fibrosa cystica may well be that these cases were almost exclusively reported by surgeons, who were apparently not as much interested in the skin changes as in the osseous manifestations of the disease For example, the first American paper dealing extensively with a classical case of osteitis fibrosa cystica disseminata, by the surgeon J J Morton, does not mention the presence of pigmented areas In the published photograph of the patient, however, they are visible on the right side of the pelvis The contours of the pelvis and of the large curvatures of the femora of this patient are identical with the contours of the coresponding bones shown in the pictures of osteitis fibrosa cystica disseminata recently published by Falconer and Cope These cases also display pigmented spots on the most involved parts

Areas of pigmentation similar to those in Addison's disease may even be found in the mucous membranes of the mouth and lips This rare type of mucous membrane pigmentation may appear in cases where the bone involvement results in a large epulis formation of the lower mandible (Oddo, our case V, Albright, personal communication) The bone involvement of the mandible with pigmentation of the mucous membranes of the mouth is also indicative of the close relation of the pigmented areas to the fibrocystic bone involvement One is led to the same conclusion by the observation that in unilateral cases of osteitis fibrosa cystica disseminata, café au lait spots and pigmented areas are confined to the side of bone involvement (Goldhammer, Borak and Doll) Since neurofibromatosis, hyperpigmented areas, and fibrocystic bone changes occur together, it seems justifiable to assume that even without the appearance of neurofibromatous nodules, the hyperpigmented areas, being the expression of underlying neurofibromatosis and often the sign of simultaneous fibrocystic bone changes, are sufficient evidence of the concurrence of both conditions, neurofibromatosis and osteitis fibrosa cystica disseminata

Histological features common to bone fibroma in neurofibromatosis and to the fibromatous growth of osteitis fibrosa cystica In both bone lesions fibrous tissue prevails The osseous and cartilagenous elements found in the fibrous growth result partly from displacement of osseous tissue by the fibromatous growth and

partly from slow new formation of bone The fibromatous growth in both instances take place in osseous tissue and is closely interwoven with the independent ana- and katabolism of this tissue There is, however, neither in the small fibroma nor in the most extensive fibromatous growth of osteitis fibrosa cystica disseminata, any sign of primary bone disease manifesting itself by osteoclastic bone resorption (osteoclastomas) or by abnormally increased new formation of bone In both instances only a few osteoclasts and a normal amount of osteoblasts are demonstrable in the histological specimen These features indicate that in both instances the ingrowing fibrous tissue is the primary cause of the bone lesions and not the result of a primary metabolic or anatomical disorder of the osseous tissue

The fibrous tissue has in the bone fibroma as well as in the fibrous masses of osteitis fibrosa cystica the tendency to undergo a collagenous or myxomatous change Cyst formation may occur not only in osteitis fibrosa cystica disseminata, it is also found to a smaller extent in isolated bone fibroma The same, only on a smaller scale, holds true for the presence of hemosiderin deposits as a result of an occasional bleeding into the fibroma and for the formation of foreign body giant cells

In the fibrocystic bone lesions in neurofibromatosis and in the extensive fibrocystic masses in osteitis fibrosa cystica no nerve tissue is found The absence of nerve elements in the fibrous masses of osteitis fibrosa cystica may be held up as the main argument against the theory of its neurofibromatous origin Such an objection is not justified, however, since in the bone fibroma of neurofibromatosis nerve elements are also not demonstrable The absence of nerve tissue may even be noted in cutaneous neurofibroma This phenomenon caused Marie and also Chauffard to suggest as early as 1896, changing the name of neurofibromatosis to "fibromatose pigmentaire" (see page 107) The absence of nerve elements in a fibromatous growth cannot be used as an argument against its neurofibromatous origin, however, since Masson (see page 109) has demonstrated that the nerve structure, the schwannoglial lineage, which caused the fibromatous growth may disappear, leaving the fibroma "aneurific" Masson called attention to the "whorls" of spindle cells occurring in some areas of these aneurific fibromas Such whorl formation suggests that in the center of a whorl a nerve fibre has been present whose schwannoglial elements induced the fibrous growth The whorl of the cell remained, but the nerve fibre in its center has disappeared Such whorl formation of spindle cells is observed in neurofibromatous nodules as well as in bone fibroma and in some areas of fibrous masses in osteitis fibrosa cystica (compare histological reproductions in Carrière and Huriez, picture 26, p 91 with Uhlmann and Grossmann, p 229), also Lichtenstein and Jaffe, Fig 3A, p 788) The whorls of spindle cells are the hallmarks of neurofibromatosis *Where whorling is found in strains of fibrous tissue in a fibromatous growth its neurofibromatous origin is suggested* For this reason their presence in the fibromatous tissue of osteitis fibrosa cystica gives, in addition to the clinical findings discussed above, further histological confirmation of the pathogenetic relation of osteitis fibrosa cystica disseminata to neurofibromatosis,

both first described by von Recklinghausen *The small fibrocystic lesion of a single bone occasionally found in neurofibromatosis and the enormous tumor-like fibrous growth in severe cases of osteitis fibrosa cystica disseminata may be analogous as regards size and extension to a small cutaneous fibroma and the disfiguring fibrocystic grows known as elephantiasis neurofibromatosa*

Summary 1 Cases of simultaneous occurrence of nodular cutaneous neurofibroma, pigmented areas (café au lait spots), and osteitis fibrosa cystica disseminata in one patient are collected from the literature The occurrence of these symptoms of both rare diseases in one person is not mere coincidence, but is evidence of the relationship of neurofibromatosis to osteitis fibrosa cystica

2 It is believed that hyperpigmented areas (café au lait spots and brown blotces), being the expression of underlying neurofibromatosis even without the appearance of neurofibromatous nodules, are sufficient evidence of the concurrence of both conditions, neurofibromatosis and osteitis fibrosa cystica

3 The histological features common to bone fibroma in neurofibromatosis and to osteitis fibrosa are discussed It is stated that nerve elements are not present in the histological specimens of fibromatous bone lesions in both conditions, yet whorling of spindle cells is found in the bone fibroma in neurofibromatosis as well as in some areas of the fibrous tissue in osteitis fibrosa cystica localisata and disseminata These whorls of cells are also present in cutaneous neurofibroma They are indicative of the neurofibromatous genesis of a fibroma because in the center of such whorls a nerve fibre with schwannoglia was once present and initiated the fibrous growth Their presence also in some areas of the fibrous tissue in osteitis fibrosa cystica localisata and disseminata gives additional histological confirmation to the theory that the pathogenesis of neurofibromatosis (Recklinghausen) and that of osteitis fibrosa cystica localisata and disseminata are related

VI ENDOCRINE SYMPTOMS IN NEUROFIBROMATOSIS AND OSTEITIS FIBROSA CYSTICA DISSEMINATA (RECKLINGHAUSEN)

Precocious Puberty and other Endocrine Symptoms in Osteitis Fibrosa Cystica Disseminata Albright, Butler, Hampton, and Smith have called attention to the symptoms of precocious puberty occurring in some patients with osteitis fibrosa cystica disseminata and brown pigmented spots of the skin These authors report five females with these symptoms and add nine other cases reported earlier in the literature Weil (1922), Gaupp (1932, reporting two cases), Priesel and Wagner (1932, quoting Salzer's case), Stalmann (1933, reporting two cases), Snapper and Parisel (1933, case reported as xanthomatosis ossium), Goldhammer (1934), and McCune (1937) were the first to mention precocious puberty together with osteitis fibrosa disseminata and pigmented spots Falconer and Cope add two cases of their own, one is a male and one in a female, quoting eight additional cases from the literature since 1937 These authors demonstrate that sexual precocity in osteitis fibrosa cystica disseminata may also occur in males and is best discovered in these male cases by the precocious skeletal development The precocious development of bones (epiphyseal union) is generalized and not at all confined to those bones which display localized or disseminated

osteitis fibrosa cystica Falconer and Cope called attention to other endocrine features which may occur in cases of osteitis fibrosa cystica disseminata Acromegalic features with incomplete hemianopia were observed in their Case 1 and in Coleman's case (1938), also with bitemporal hemianopia In this case the acromegalic features are believed to be the result of pressure due to bony overgrowth of the skull Moehlig and Schreiber described gynecomastia with feminine distribution of hair in a boy of 16 years who displayed characteristic lesions of osteitis fibrosa cystica disseminata One case described by Albright, Scoville, and Sulkowitch also had gynecomastia None of the authors gave any explanation of any etiological connection of the endocrine symptoms, especially of the precocious puberty, with osteitis fibrosa cystica disseminata

Endocrine Symptoms in Neurofibromatosis In the preceding sections, it has been attempted to demonstrate that the pathogenesis of osteitis fibrosa cystica disseminata is related to that of neurofibromatosis This conception would acquire further evidence if endocrine symptoms similar to those observed in osteitis fibrosa cystica disseminata, especially precocious puberty, were reported as occurring in cutaneous neurofibromatosis alone (pigmented areas with and without neurofibromas) Furthermore, such a concurrence of endocrine symptoms and cutaneous neurofibromatosis would offer an explanation of the causal relation of endocrine symptoms to osteitis fibrosa cystica disseminata through a common pathogenic principle, i e , neurofibromatosis

In searching for such evidence we find that endocrine symptoms in cutaneous neurofibromatosis, especially when accompanied by areas of hyperpigmentation, are not infrequently reported in the literature The endocrine features in these cases of neurofibromatosis resulted from the following causes

I *Hypertrophy or sclerosis of adrenals and pituitary*

(A) *Adrenals*

Chauffard, 1896 (adenoma of both adrenals, the left adrenal tumor was so large that it enveloped the pancreas)

Merk, 1905 (neurofibromatosis and pigmentation, changes in left adrenal found on autopsy)

Raymond and Alquier, 1908 (neurofibromatosis and pigmentation, sclerosis of both adrenals and pituitary with nodular hyperplasia)

Muto 1910 (neurofibromatosis and pigmented spots, infiltration of both cortical zones of the adrenals, histological changes in pituitary and thyroid)

Vignolo Lutati, 1911 (sclerosis of both adrenals and neurofibromatosis)

Saalmann, 1913 (neurofibromatosis, hypernephroma originating in a suprarenal rest in the liver)

Bosquet, 1913 (cutaneous neurofibromatosis, right suprarenal almost entirely transformed in epithelial tumor)

Kawashima, 1911 (cutaneous neurofibromatosis, kyphoscoliosis, tumor of suprarenal medulla)

Tucker, 1924, Szand, Kennedy, and Miskaley, 1925, Stark, 1928 (discussion of Recklinghausen's disease with endocrine symptoms)

(B) *Pituitary* (acromegaly, hypogonadism, gynecomastia)

Wolfsohn and Marcuse, 1910 (neurofibromatosis and acromegaly)

Minkowsky, 1911 (acromegaly and neurofibromatosis)

Ormond, 1920 (neurofibromatosis and acromegaly)
Barber, 1922 (Ormond's case neurofibromatosis and acromegaly)
White, 1926 (Recklinghausen's disease with pituitary symptoms)
Freund, 1929 (neurofibromatosis and acromegaly)
Louste, Caillaux, and Darquier, 1925 (Recklinghausen's disease and acromegaly)
De Castro, 1934 (neurofibromatosis and acromegaly)
(1) *Hypogonadism*
Lier, 1914 (neurofibromatosis, bilateral hemianopia)
Hoffmann, 1929 (neurofibromatosis, hypogonadism)
Bohn, 1923 (neurofibromatosis, hypogonadism)
Ehrmann, 1924 (neurofibromatosis, hypogonadism)
Freund, 1929 (Case 3, neurofibromatosis and hypogonadism)
Case I of this paper, p 113

II *Neurinomas of the adrenals*
Maini, 1925 (neurofibromatosis and neurinoma of adrenals)
Martz, 1933 (neurofibromatosis of sympathetic nerve with participation of brain and pituitary)
Rosenthal and Willis, 1936 (neurofibromatosis associated with chromaffin tumors)

III *Pressure effect upon the third ventricle or upon the pituitary by a central neurofibroma or by hydrocephalus due to central neurofibroma*
Barbé and Delay, 1939

IV *Congenital anomalies of the brain tissue occurring in neurofibromatosis*
Heuneberg and Koch, 1903 (central neurofibromatosis)
Christin and Neville, 1920 (central neurofibromatosis)
Winkelbauer, 1927 (skull changes in neurofibromatosis)
Fulton and Bailey, 1930 (Recklinghausen's disease with tumors of the 3rd ventricle)
Harbitz, 1932 (central neurofibromatosis)
Martz, 1933 (neurofibromatosis of sympathetic system and brain)
Zimmer, 1936 (central neurofibromatosis)

Precocious puberty in neurofibromatosis Reported cases of precocious puberty which simultaneously exhibit cutaneous neurofibromatosis are not included in this review of patients suffering from cutaneous neurofibromatosis and endocrine symptoms Four cases are reported in the literature which displayed symptoms of precocious puberty, 4 having pigmented spots, 3 pigmented spots and cutaneous fibroma Shaw demonstrated in 1922 a sexually precocious boy of 15 who was brought to the hospital because of obesity, with the large type of pigmented patches and some soft subcutaneous nodules One was removed and later reported as neurofibroma Bilateral optic atrophy was present X-ray examination showed a shadow and flattening between the anterior and posterior clinoid processes

Mallam (1922), stimulated by the report of Shaw's case, described and published photographs of a similar case of association of neurofibromatosis with precocious puberty and endocrine symptoms A boy, 8 years of age, had grown and developed enormously from his fourth year At eight he weighed 119 pounds and was 4 feet 10½ inches tall "The sexual organs were greatly developed for a child of eight, the pubic hair fairly well grown, the voice was low-pitched, and he had developed a troublesome tendency to masturbate" The

skin presented the signs of neurofibromatosis Patches of pigmentation were seen, and many sessile masses of fibrous material could be felt on the trunk, flank, and shoulders The hair was strong and coarse, and the nails brittle His mind was acute, but at games he was bad He suffered from headaches and fatigue His bones were large X-ray examination showed a well-defined sella turcica of normal size The author believed the case to be one of an anomaly of the pineal gland

H F de Vries (1930) describes a girl with Recklinghausen's neurofibromatosis, pigmented blotches, and precocious puberty The girl at nine years of age was menstruating and sexually fully developed She had large breasts and sexual hair like an adult female Her height was twice that of a normal child her age She was mentally backward Hemianopsia was found

Sainton and Bailast published an observation on "syndrome fruste de neurofibromatosis [pigmented blotches], macrogenitosomie et glaucome" It has not been possible to secure the original French article, so details cannot be reported at this time The title, however, tells us that a patient demonstrated signs of neurofibromatosis of the skin, together with enlargement and probably early development of the genital organs

Mosse and Cavalié report a case of cutaneous neurofibromatosis with simultaneous involvement of the pituitary as well as the pineal gland Kirch describes a patient with neurofibromatosis on whom a cyst of the pineal gland was found

It is thus demonstrated that neurofibromatosis, café au lait spots, and brown blotchy pigmentation have been observed to be associated with premature sexual development Furthermore, it is certainly not mere coincidence that precocious puberty is described also in some cases of osteitis fibrosa cystica disseminata exhibiting café au lait spots and blotchy pigmented areas It seems most probable that the brown pigmented areas which in both instances result from neurofibromatous changes of the finest skin nerves beneath the brown spots (see Section II of this paper) are indicative of the causal connection of endocrine symptoms as well as of the fibrous changes in the bones in osteitis fibrosa cystica with the pathogenetic principle of neurofibromatosis Since in some cases of osteitis fibrosa cystica disseminata not only precocious puberty or acromegalic features and gynecomastia are observed, the scope of endocrine disturbance in the sexual sphere is as wide as that observed in cases of neurofibromatosis without osseous pathological involvement

Pathology of Endocrine Symptoms in Neurofibromatosis and Osteitis Fibrosa Cystica Disseminata (Recklinghausen) The underlying anatomical changes which result in endocrine features are certainly different in different cases of pure cutaneous neurofibromatosis as well as in osteitis fibrosa cystica disseminata but the underlying pathogenic principle in both instances is most probably the same (i e, anatomical changes connected with [illegible] pathology) As discussed above, hyperfunction or decreased [illegible] of glands or tumors may be the result of anatomical changes [illegible] as well as the result of increased intracranial pressure by [illegible] fibromatous tumor It may be a neurofibromatous tumor of the gland

question itself Only autopsy material will be able to decide the underlying anatomical situation in these conditions

Only one case of osteitis fibrosa cystica disseminata with precocious puberty has come to necropsy (this patient was first reported by Freedmann and later by Albright and coworkers) The child died in the Floating Hospital (unit of the New England Medical Center) of virus pneumonia Through the courtesy of Dr James A Baty, I was invited to see the child before the intercurrent infection happened The clinical features were still the same as described by Freedmann At autopsy no glandular tumor was found, but there was an abnormal condition in the region of the third ventricle (personal communication from Dr MacMahon) The histological examination of the brain revealed changes in the third ventricle which suggested an accessory nucleus in this region (Dr MacMahon will describe the findings in a special publication)

The presence of a congenital anomaly of the brain tissue would concur with the features discussed above (Section IV) which occur in neurofibromatosis Endocrine symptoms such as precocious puberty, acromegalic features, or gynecomastia may result from such a congenital abnormality of the brain tissue located in the third ventricle

The occurrence of a congenital structural anomaly of the brain tissue and the presence of pigmented spots of the skin in a case of osteitis fibrosa cystica disseminata tends to increase the evidence for our belief that all these symptoms have a common pathogenesis, which is probably neurofibromatosis

Summary Case reports are quoted from the literature in which neurofibromatous nodules, café au lait spots, and brown pigmented areas were observed together with endocrine symptoms The anatomical changes which cause endocrine symptoms in neurofibromatosis are discussed on the basis of autopsy findings reported in the literature Special attention is called to four cases combining symptoms of precocious puberty, neurofibromatous nodules, and café au lait spots The observation of similar endocrine symptoms, especially the concurrence of precocious puberty and pigmented blotches of the skin in neurofibromatosis and also in osteitis fibrosa cystica disseminata offer additional corroboration of the belief that the two disturbances are related This suggests that the anatomical structures which underly the endocrine symptoms in cases of simple neurofibromatosis may be the same in cases of osteitis fibrosa cystica disseminata (Recklinghausen)

Case of Osteitis Fibrosa Cystica Disseminata with Precocious Puberty *Case VI* (No 306275), a ten-year-old Italian girl was first seen at the age of six months at the Boston Dispensary and Floating Hospital (unit of the New England Medical Center) This case was reported by H J Freedmann and later by Albright, Butler, Hampton, and Smith

Case History (courtesy of Dr Freedmann) Birth was normal There was no family history of importance The infant was first seen at the age of six months because of diarrhea, which was successfully treated

Precocious Sexual Puberty At the time of this first admission, the infant had already menstruated, menstruation having started at the age of four months

During the third year, periods recurred every two months The menstrual periods thereafter occurred every three weeks irregularly Occasionally there was a steady flow for as long as three weeks At the age of six months the external genitalia, especially the clitoris (1 cm) were enlarged At the age of one and a half years, the breasts became larger and the areolae displayed a brownish color At this time a luxurious growth of pubic hair was noticed The sexual characteristics were those of a normal adult From the age of eighteen months on, the child masturbated

Pigmented blotches Areas of brown pigmentation first occurred on the right cheek The pigmentation did not spread until the sixth month, when another blotch was noticed on the left leg Later, pigmented areas appeared on the left buttock, left thigh, left knee, and left ankle Smaller spots appeared also on the trunk At the beginning, the pigmented areas were café au lait in color, later they became deep brown

Mental Development The child sat up at nine months, walked at twenty-two months She could not talk until five years of age She never attended school She frequently had temper tantrums, in which she screamed, pulled her hair, and scratched her face

Skeletal Changes Pain was not noted until the age of three at which time she fractured a leg Later, spontaneous fractures occurred several times Deformities of her thighs (lateral bowing) became visible and there was also asymmetry of her cheeks Walking became difficult, but not because of pain There was no complaint of spontaneous pain, the places of former fractures being only slightly painful She died at the age of ten of acute intercurrent pneumonia

Laboratory Findings Calcium 11 1 mgm %, phosphorus 3 4 mgm %, total cholesterol 175 mgm %, phosphatase 38 Bodansky units Hormone studies (Dr Werthesson) showed follicle-stimulating hormone present in the blood In 24-hour urine estron 22 gamma, estriol 5 gamma, androgen value equals 20 units (increased values for female sex hormone)

X-Ray Findings (at nine years) A spotty cyst-like involvement of almost all the bones of the skeleton was seen There was no generalized decalcification Several healed fractures were present The left femur showed "boomerang" shape, the right femur a healed fracture The cyst-like areas were seen on the skull, long bones, scapulae, even on some small bones of the hands and feet The pelvis and also some vertebrae showed cyst-like areas The shafts of the long bones were expanded by the lesions at some areas

Autopsy Findings The autopsy (Dr Osgood) confirmed the clinical diagnosis of osteitis fibrosa cystica disseminata (earlier biopsy report by Dr Sidney Farber in Albright and coworker paper) The most important findings of the autopsy (personal communication of Dr MacMahon) were 1) The parathyroids were not enlarged, 2) No visible anatomical involvement of the adrenals, pituitary or other endocrine glands was found, 3) There was abnormality in the area of the third ventricle, which was considered on histological examination to be a congenital anomaly exhibiting an accessory nucleus in the subthalamic area (Dr MacMahon will publish these findings in a separate, detailed paper)

FINAL SUMMARY

On the basis of Masson's investigations it is demonstrated that fibromatous growth in neurofibromatosis may occur without later evidence of the originating schwannoglial lineage (aneuritic fibromas) Whorls of spindle cells, if present in the fibrous tissue, are indicative of its neurofibromatous origin

Pigmented areas of skin with sharp borders (café au lait spots or geographical map-like brown blotches) are the result of structural changes of the underlying finest skin nerves Pigmented blotches of the café au lait or geographical map-like variety are as much an indication for the diagnosis of neurofibromatosis as the cutaneous neurofibromatous nodule itself

Fibrocystic involvement of localized areas of the skeleton, especially of the long bones but also of other portions, occurs in neurofibromatosis together with café au lait spots and cutaneous neurofibromas Osseous fibroma are not only found as so-called "subperiosteal cysts," but also as fibroma located in the trabeculated spaces of the long bones The microscopic examination of the osseous fibroma does not reveal nerve structures within the fibroma, but whorls of spindle cells are occasionally found as "hallmarks" of its neurofibromatous origin

Hyperfunction of the parathyroid as a pathogenic principle is discussed The different clinical symptomatology of hyperparathyroidism with generalized decalcification and fibrocystic lesions of the skeleton and osteitis fibrosa cystica localisata and disseminata (fibrous dysplasia of bone) are described It is pointed out that the outward appearance, the clinical features, and the cause of death are different in the two entities Recklinghausen's original cases are analyzed The first two described as fibrous osteitis (Cases 5 and 6), exhibit the features of osteitis fibrosa cystica disseminata Therefore, the name of Recklinghausen should be connected with osteitis fibrosa cystica disseminata and not with primary hyperparathyroidism Analogous to observations on cases with diffuse malacic bone disease, secondary reactive hyperplasia of the parathyroids may also occur in rare instances in osteitis fibrosa cystica disseminata, but without the progressive generalized symptoms of primary hyperparathyroidism

On the basis of reports of simultaneous occurrence of nodular cutaneous neurofibroma, pigmented areas of the skin, and osteitis fibrosa cystica in one patient, a coherence of neurofibromatosis and osteitis fibrosa cystica is suggested, since the occurrence of these symptoms of two rare diseases in one person cannot be mere coincidence It is believed that hyperpigmented areas (café au lait spots and brown blotches), being the expression of underlying neurofibromatosis even without the appearance of neurofibromatous nodules, are sufficient evidence of the concurrence of both conditions, neurofibromatosis and osteitis fibrosa cystica It is stated that nerve elements are not present in the histological specimens of fibromatous bone lesions in both conditions, yet "whorls" of spindle cells are found in the bone fibroma in neurofibromatosis as well as in some areas of the fibrous tissue in osteitis fibrosa cystica localisata and disseminata These whorls of cells are also present in cutaneous neurofibroma They are indicative of the neurofibromatous genesis of a fibroma because in the center of such whorls

a nerve fiber with schwannoglia was once present and initiated the fibrous growth Their presence also in some areas of the fibrous tissue in osteitis fibrosa cystica localisata and disseminata gives additional histological confirmation to the theory that the pathogenesis of neurofibromatosis (Recklinghausen) and that of osteitis fibrosa cystica localisata and disseminata are related [4]

The observation of similar endocrine symptoms, especially the concurrence of precocious puberty and pigmented blotches of the skin in neurofibromatosis and also in osteitis fibrosa cystica disseminata offers additional corroboration of the belief that the two disturbances are related This suggests that the anatomical structures which underly the endocrine symptoms in cases of simple neurofibromatosis may be the same in cases of osteitis fibrosa cystica disseminata (Recklinghausen)

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[4] Since this article went to press, Dr A J Ackerman (Pulmonary and Osseous Manifestations of Tuberous Sclerosis, American Journal of Roentgenology, 51 315-325, March, 1944) has called attention to osseous and pulmonary manifestations of tuberous sclerosis In this paper he has included x ray pictures of bone cysts occurring in tuberous sclerosis of the brain identical to osteitis fibrosa cystica disseminata Since tuberous sclerosis is considered a manifestation of the brain related to neurofibromatosis, the simultaneous occurrence of fibrocystic bone changes in the same disease is very much in accord with our conception that osteitis fibrosa cystica disseminata is also of neurofibromatous pathology

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FILARIASIS DUE TO WUCHERERIA BANCROFTI

L EVERARD NAPIER

CONTENTS

HISTORICAL

Although filariasis in its grosser manifestations was mentioned by ancient Indian writers, the term 'elephantiasis' was apparently first used by Celsus to indicate leprosy, and later by Galen to indicate both leprosy and true elephantiasis A third disease, Madura foot, was also generally confused with leprosy and elephantiasis, until about the eighteenth century In 1750, Hillary gave a full and lucid account of the elephantoid leg, wherein he clearly differentiated this disease from leprosy The classical researches of Danielssen and Boeck in 1848 on leprosy and those of Vandyke Carter in 1860 on mycetoma, established clearly the true nature of those two diseases, and their distinction from one another and from filariasis

EPIDEMIOLOGY

Geographical distribution

Of the human filarial parasites, *Wuchereria bancrofti* has the most extensive distribution in the tropics and sub-tropics and occurs in regions from about 42°N to about 38°S in the eastern hemisphere and from about 30°N to 30°S in the western hemisphere

In America, the infection is common in Central America, in the West Indies, in British, Dutch and French Guiana, Venezuela, Brazil, Peru, and Colombia In the United States a considerable focus of infection, probably originally introduced from Africa, was discovered in South Carolina some years ago, but no fresh cases have been reported in recent years, it probably does not occur elsewhere

It is common on the west coast of Africa, in Madagascar and the neighbouring islands of Mauritius and Réunion, in East Africa, and in Egypt and North Africa

In Europe, it is reported to occur in Spain (Barcelona), Hungary, and Turkey

In Australasia, it is common in New Guinea, Papua, and other islands, and it occurs along the northern and eastern coasts of Australia It is extremely common throughout the Pacific islands, such as Samoa and Friendly Islands, Fiji, and the Gilbert and Ellice groups of islands

In Asia, it is especially prevalent in Arabia, India, Ceylon, Burma, the Phillippines and the islands of East Indies, southern China, and southern Japan In some of these areas over 80 per cent of the population are infected

In India, the infection is extremely prevalent, but it is more or less confined to the coastal regions and to areas along the banks of the important rivers West Bengal, Orissa, Travancore, Cochin and Malabar are the most heavily infected areas (microfilaria-rate over 20 per cent to over 30 per cent) All these are low flat countries that have a high rainfall, they are water-logged for many months each year, and the temperature and humidity are both high for over half the year, conditions are, therefore, very favourable for the breeding of mosquitoes and for the transmission of the infection The moderately infected regions (microfilaria-rate between 5 and 20 per cent) include the rest of the east coast of India, East Bengal, the United Provinces, Bihar, and certain areas in the Bombay Presidency, such as Surat, Ahmedabad and Thana Mildly endemic areas include the whole of the Deccan plateau, the Central Provinces, and Assam However, the intensity of infection is not uniform even within a single endemic area, for instance, in Calcutta the eastern wards of the city show a much heavier infection rate than the central or western wards

All the areas lying north of a line drawn from Karachi to Delhi are free from the infection, these include the Punjab, Sind, the North-West Frontier Province, Kashmir, and Rajputana Elevated regions, above 4,000 feet, are also free from infection

Epidemic status

It is essentially an endemic disease, and any rise and fall in the incidence of the disease will as a rule only take place over a number of years Rises in incidence are usually associated with increases of population, or with an increase in the Culex population through ill-advised engineering or agricultural undertakings, or through a deterioration in the sanitation of the area (*vide infra*), conversely, any decline in incidence can usually be traced to improvement in sanitation, especially with reference to anti-mosquito measures, or more rarely to reduction in the human population

In most places the disease has already found its own level so that, as occasionally happens, when an infected group of individuals from a highly endemic area migrate or are transferred to an area of low endemicity, there is seldom more than a temporary increase in the infection rate in the local population, if any increase at all is noted On the other hand, when an uninfected population is transferred to an endemic area, the immigrants will in the course of years[1]

[1] This is the usual experience, but when a non infected group lives in close association with a hyper infected population, the intensity of the infection to which they are subjected may lead to a much earlier development of the disease amongst the newcomers

become infected, but their arrival will probably not lead to a general rise in the incidence of the disease in the area, as occurs in the case of most epidemic diseases.

Seasonal distribution

In highly endemic areas, infection takes place at any time of the year, but in the areas of moderate and low endemicity it will only take place at a time when the temperature, humidity and other conditions are favourable (*vide infra*) However, the time taken for the development of symptoms is so variable and usually so long that the onset of symptoms bears little time relation to infection In Calcutta the highest onset period was during the monsoon, July to September, there were 40 per cent more fresh cases than in the cooler-weather months, October to February But this probably indicates nothing more than a lower resistance on the part of the patient at this time of the year

Age, sex, race and occupation

No definite relation appears to exist between the incidence of infection and the age or sex in a population Filarial surveys of endemic areas in India, carried out by Rao (1924–1941), have shown that the age incidence of lymphatic obstruction depends on the intensity of the infection to which the people are subjected Thus, in hyperendemic areas,[2] elephantiasis may commence even at as early an age as 5 years, and, in one case, microfilariae were detected in the blood of a baby of 14 months In moderately endemic areas, the lesions commence generally between the ages of 14 and 16, and in areas of low endemicity between 20 and 25 years In general the incidence of infection in women is less than in men This may be partly due to their conditions of living and their mode of dress

No special correlation between the incidence of infection and the race or occupation of the individual has been noted In Calcutta, a town of moderate endemicity, it is very rare for the disease to be found amongst European sojourners, but it is not uncommon amonst those who have lived there all their lives, and it is as common amongst the poorer Anglo-Indians as amongst the Indians

AETIOLOGY

Historical

The discovery of microfilaria in the hydrocele fluid of a filarial patient was first made by Demarquay in 1863 in Paris In 1866, Wucherer independently discovered a microfilaria in the chylous urine of a filarial patient in Brazil He continued his investigations and later

[2] Endemic areas can for convenience by classed as
(a) *hyper-endemic areas—microfilaria rate 30 per cent or more,*
(b) highly endemic areas—microfilaria rate 20 per cent but less than 30 per cent
(c) moderately endemic areas—microfilaria rate less than 20 but over 5 per cent, and
(d) areas of low endemicity—microfilaria rate 5 per cent or less, but an occasional positive finding

obtained comparable findings in several cases of haematochyluria, a similar observation was recorded by Salisbury in 1868 Lewis working in Calcutta made the important discovery in 1872 that the microfilaria which was present in the chylous urine occurred also in the blood and lymph of persons suffering from elephantiasis, and in his subsequent investigations he showed that the embryo invades the thoracic region of the mosquito and there undergoes development, but he did not study the subsequent stages of development as he could not keep his mosquitoes alive for more than a week The presence of microfilariae in chylous ascitic fluid was first observed by Winckel in 1876, and in the same year the adult filarial worms were discovered by Bancroft

About the same time, Manson carried out pioneer investigations in filarial infection in China and present knowledge of the subject is mainly due to his classical researches on the transmission and the pathology of the disease Manson made the memorable discovery in 1878 that the mosquito *Culex fatigans* was the carrier of filarial infection He demonstrated that the filarial embryo developed inside the mosquito in seven days In 1900, Low demonstrated that the infective larva escaped from the proboscis of the mosquito on to the skin at the time of biting Since then several investigators have carried out extensive researches dealing with many important aspects of the infection, *e g* Manson-Bahr (Bahr, 1912), investigating filarial infection in the Fiji Islands, showed that the transmitter of this infection in this region was *Aedes variegatus* var *pseudo-scutellaris*, and that *Culex fatigans*, which is the important transmitter in other endemic areas of the world, is not so efficient in these islands He was also the first to show that the microfilariae in the blood in Fiji exhibited no periodicity and that the nocturnal periodicity of the embryo was dependent upon the biting habits of the intermediary host

Causal organism

The adult *Wuchereria bancrofti* are white hair-like translucent worms having a smooth cuticle The male and the female worms live coiled together in the dilated lymphatics, the male being considerably smaller than the female The head is rounded and is separated from the body by a neck-like constriction It it provided with two rows of small sessile papillae The mouth is without lips and unarmed The oesophagus has no bulb-like swelling at its posterior extremity The anus is situated close to the posterior extremity of the worm

Males measure from 25 to 40 mm in length and about 0 1 mm in breadth The tail is specially curved ventrally The cloaca is about 0 1 mm from the posterior extremity The testis is not coiled and terminates as a snowdrop-like process (Leiper) The accessory piece or gubernaculum which is chitinous is crescentic There are two spicules of unequal length The long one is cylindrical, expanded proximally and tapering distally, ending in a glans like swelling The short spicule is of the same diameter throughout, gutter-like and coarsely marked, especially near its distal extremity There are nine pairs of caudal papillae which are pedunculated, five pre-anal and four post-anal in position The caudal alae are sometimes indistinct (Maplestone and Rao, 1939)

Females measure from 30 to 100 mm in length and from 0 2 to 0 3 mm in breadth The tail tapers gradually, the tip is rounded The anus opens about 0 2 mm from the tip of the tail The vulva opens on the ventral surface about 0 6 mm to 1 3 mm from the anterior end The vagina is a muscular tube forming a loop with a pyriform enlargement and ends in the uterus, the distal end of which is generally found filled with fully extended embryos ready to be discharged At its proximal end, the uterus is divided into two branches which

occupy the greater portion of the body and each terminates towards the tail end in an ovary Each branch of the uterus contains eggs and embryos in various stages of development

The ova and embryos These are found in the posterior end of the uterus Their dimensions vary according to the stage of their development, when fully developed they measure about 40 microns in length and 25 microns in breadth The ovum does not possess a true shell, but only a membrane which becomes stretched to form the so-called sheath of the microfilaria

The measurements of the individual microfilariae (embryos) of *Wuchereria bancrofti* in ordinary thick smears, when plotted on graph paper, exhibit a smooth curve, and there is no marked difference in their measurements in the wet and the dry states, the average length of the embryo itself is 290 microns, the breadth 6 to 7 microns, while the length of the sheath is 359 microns (Iyengar, 1939)

The embryo shows well-marked cuticular striations The cephalic space is generally smaller than the breadth of the embryo in this region The tail tapers gradually to a rounded tip and is free from nuclei

Life-cycle of the parasite

The adult filarial parasites live in the lymphatics of man, mainly in those of the pelvic region They are known to live there for a considerable period of time without producing obstruction to the lymphatic circulation The gravid female discharges embryos periodically, these embryos reach the blood stream and circulate there The embryos exhibit a nocturnal periodicity[3] in the blood stream, except in Fiji and certain other Pacific islands where they show no special periodicity They do not develop further in the blood, but are taken up by the intermediate host, the mosquito, where the next stage of development occurs

Ordinarily, a drop (20 cmm) of peripheral blood of an infected individual may contain anything up to 600 embryos It has been found that, while a moderately high concentration (about 15 embryos per drop of blood) is necessary for the successful transmission of the infection, a much higher concentration of microfilariae, *viz*, 100 or more embryos per drop, is fatal to the mosquito

[3] *Microfilarial periodicity* The maximum number of microfilariae is found between the hours of 10 p m and 2 a m, and never during the day This periodicity is a device on the part of the filarial worm (or of Nature) to aid propagation of species, as it is only observed in countries where the main mosquito vector is a night-feeder In Fiji, *Aëdes variegatus*, which is a diurnal feeder, is the important vector, and the microfilariae are found in the blood throughout the 24 hours in this and other Pacific islands Many theories have been put forward to explain the mechanism of this periodicity—that it is due to light, directly repelling the embryos or adversely affecting their activity, to the inactivity of the host at night, to chemotaxis from the bite of the mosquito, to defective oxygen supply, or to mid-day parturition of the worm and the daily death of the microfilariae—but no theory is entirely satisfactory The ingenious, though unlikely, theory regarding mid-day parturition (Lane, 1933)—which itself requires further explanation—has been disproved by several workers who have shown that even in another host the life of the microfilaria is over a week

If the host changes his habits and sleeps during the day, the microfilariae that he harbours will change their periodicity correspondingly in about three days

The development of the filarial embryo in the intermediate host, the mosquito, may be briefly described as follows

As the mosquito feeds on the blood of an infected individual, the embryos (microfilariae) are taken in by the mosquito and enter its stomach With the progress of digestion in the stomach, the blood plasma becomes thickened At this stage the embryos escape from their sheaths and enter the thoracic region of their mosquito host It has been shown by Iyengar (1939) that within ten minutes most of the embryos enter the thorax and lie in between the thoracic muscle fibres, where at first they are comparatively inactive After two days the first-larval-stage embryos measure about 124 to 250 microns by 10 to 17 microns Many changes take place in the structure of the embryos, and the tail becomes reduced to a stump (sausage stage) After the third day, the development of the body cavity, oesophagus and the anus takes place, and at the end of seven days the larvae (second stage) measure 225 to 300 microns by 15 to 30 microns Caudal papillae are now observed

During the second week, moulting occurs and under optimum conditions the metamorphosis is complete by the tenth or eleventh day The infective third-stage (filariform) larvae which now measure 1500 to 2000 microns by 18 to 23 microns show an alimentary canal and a tri-lobed tail They leave the thorax, migrate to the proboscis, and eventually reach the interior of the labium They are generally seen to move in pairs When the mosquito feeds, the larvae escape at the junction of the labium with the labella and enter through the puncture made by the mosquito or even through the unbroken skin

The larvae find their way into the peripheral lymphatics Their subsequent progress and eventual fate will depend to a great extent on the host's reactions, but under conditions of perfect symbiosis the cycle will be completed as follows The larvae migrate centripetally and eventually reach the large lymphatic trunks where, having developed into male and female adults, they mate The female parturates and the microfilariae are carried *via* the lymphatic trunks into the subclavian veins and the systemic circulation

This is the outline of the cycle as it occurs when symbiosis is perfect and it accounts for none of the pathogenesis associated with the infection when the host's tissues react to the presence of the worm, these reactions and their effect on the cycle will be described below under the heading of Pathology

It is, however, possible that in some instances after the adult worms have mated, they, or at least the females, migrate centrifugally to the lymphatics of the extremities and genitals to parturate This hypothesis—for which there is analogy but no experimental proof—would help to explain certain observed phenomena, though it is believed that these can be explained almost as well on other grounds (*vide infra*)

From the entry of the mature larvae to the appearance of microfilariae in the blood of the host is usually stated to be about one year, but there is evidence that the interval may be much longer

Correlation between filarial infection and filarial disease

It is no longer necessary to discuss this from the point of view of establishing the causal relationship between filarial infection and the various clinical mani-

festations of the disease, for the subject is only one of historical interest, as far as the commoner clinical manifestations of filariasis are concerned

Many of the early workers, *e g* Low (1908) and O'Connor (1923), noted the correlation between the incidence of filarial disease and the blood microfilaria rate in the community, and, recently, Iyengar (1938) found a positive correlation coefficient of + 0 7644 between the microfilarial rate and filarial disease in 216 localities in Travancore (India) In chyluria due to filarial infection, microfilariae are usually found in the peripheral blood, Ray and Rao (1939) found them in 78 per cent of their cases

On the other hand, most (though not all) observers have found a very definite negative correlation between blood microfilarial findings and elephantiasis in the individual In India, Acton and Rao (1930) found microfilariae in only 5 7 per cent of cases of frank filarial elephantiasis, whereas they found them in 14 7 per cent of the symptom-free population of the same area In a population in which there was a 92 8 per cent filarial disease rate, Rao (1941) found a microfilaria rate of 8 4 per cent in those with elephantiasis, against 54 3 per cent in those without it Iyengar (1938) in an investigation involving over four thousand persons, of whom over five hundred had clinical filariasis, in several localities in India found the microfilaria rate was on an average about three times as great amongst those showing no clinical evidence of the infection as amongst those with elephantiasis

The usual explanation for the higher microfilaria rate in subjects without clinical lesions, namely that the lymphatic channels are mechanically blocked by the worms and the reaction that they cause, so that no microfilariae can get into the circulation (*vide infra*), seems scarcely adequate to account for this very striking difference It seems that one must visualize a general reaction of an allergic or an antibody[4] nature on the part of the host, otherwise one would expect the worms in those areas where the blocking was as yet incomplete to provide some microfilariae On the other hand, the absence of microfilaria noted in the earliest stages of infection is almost certainly due to the immaturity of the worms and/or to their failure to mate

Conditions favourable to the development of the larvae in the mosquito

The stages of the development of the larvae of *Wuchereria bancrofti* in mosquitoes, outlined above, require a mean atmospheric temperature of about 80° F and a humidity above 60 per cent Laboratory-controlled experiments by Rao have shown that the development of the larvae in the mosquito depends directly upon temperature and humidity, the optimum conditions for the development have been found to be a combination of 80° F with 90 percent

[4] It seems possible that the microfilariae that are retained in the tissues behind the obstruction in the lymphatic vessels, or in the subcutaneous tissues, are actively destroyed and provide the necessary sensitizing (*sensu lato*) stimulus, whereas in lymph varix, chyluria, etc., the microfilariae reach the blood stream where they circulate until they are obsolete and are subjected to a gradual process of absorption with other circulating debris The observation of Iyengar (1933) that the longer the duration of the obstruction the lower the microfilaria rate would support this view

humidity Under these conditions the parasite is found to complete its full development in the mosquito within seven days Observations carried out in India (Calcutta and Cuttack) and in China have shown that the times for development in the mosquito under natural conditions vary according to the temperature and humidity, from two weeks in the summer to three weeks or over in the winter months Delay in the development of the filarial embryo in the mosquito reduces the chances of the infection being transmitted, because in many instances the embryo will fail to reach the third larval, the infectve, stage

Intermediate hosts

Culex fatigans is the common host in Egypt, India, South China, Formosa, Celebes, the East Indies, the Philippines, Australia, the West Indies, and Brazil In mosquitoes of other species and genera, the complete developmental cycle will take place and one must assume, therefore, that they are potential vectors In some instances, *e g Aedes variegatus* var *pseudoscutularis* in Fiji, these are known to be the principal vectors Craig and Faust (1943) give the following as potential vectors:—

Culex pipiens and *C pipiens* var *pallens* (Central China, Japan and Egypt), *C habilitator* (St Croix, W Indies), *C fuscocephalus*, *C whitmorei*, *C annulirostris*, *C alis* and *C vishnui* (all from Dutch East Indies and Celebes), *Aëdes aegypti* (West Africa, New South Wales, St Croix, West Indies), *Aëdes variegatus* (Pacific Islands), *Aëdes togoi* (Japan), *A taeniorhynchus* (St Croix, W Indies), *Taeniorhynchus pseudotitillans* (Malaya), *T uniformis* (Central Africa), *T justamansonia* (Brazil), *Anopheles albimanus* (Caribbean area), *A albitarsis* (Brazil), *A gambiae*, *A funestus*, *A rhodesiensis*, *A squamosus* (Sierra Leone), *A algeriensis* (Tunis), *A hyrcanus* var *nigerrimus* (Travancore), *A hyrcanus* var *sinensis* (Shanghai), *A barbirostris*, *A subpictus* (both fresh- and brackish-water types), *A pseudojamesi* (*ramsayi*), *A varuna*, *A philippinensis*, *A pallidus*, *A annularis* (*fuliginosus*), *A stephensi*, *A sundaiacus* (all in India), *A amictus* (North Queensland), *A barbirostris* var *bancrofti* (Dutch East Indies, Celebes), *A aconitus* (Dutch East Indies and Celebes), *A punctulatus* (New Guinea and Celebes), and probably *A maculatus* (Celebes)

FACTORS AFFECTING ENDEMICITY

The four essentials for transmission are,

(i) the source of the microfilaria, which is always man,
(ii) the mosquito vector,
(iii) susceptible man, and
(iv) links between (i) and (ii), and (ii) and (iii)

There is no reason to believe that race, age, or sex *per se* make any difference in the susceptibility of man to infection or in the number of microfilariae that will circulate in his blood, given therefore the source of infection and mosquitoes of a good transmitting species (of which there are many), the factors influencing the amount of filarial infection in any locality will be,

(*a*) the density of the human population,

(*b*) the density of the vector-mosquito population, and

(*c*) the length of duration of the period of effective transmission each year[5]

But, given a fixed human and a seasonally varying mosquito (*e g Culex fatigans*) population, filarial incidence will depend not so much on (*c*), but more on the length of duration of the coincidence of the favourable periods in factors (*b*) and (*c*), that is, on

(*d*) the length of duration of the coincidence between the peaks (or high plateaux) of the mosquito-incidence and favourable-temperature and humidity curves

The density of the vector-mosquito population (*b*) will depend on a number of factors which will vary according to the species concerned, but the seasonal variations in the density will also depend to a great extent on temperature and humidity, and the same ranges as in the case of factor (*c*), namely, 80° to 90° F and over 90 per cent, will certainly be favourable for mosquito breeding, but other contemporaneous factors may not be, and therefore the peaks do not always coincide

For example, in Calcutta, the most suitable period for transmission is from May to October, but the peak of the Culex curve is later in the year, so that Calcutta is an area of moderate endemicity, whereas in many coastal towns in South India, the transmission period lasts almost throughout the year, and such places are hyper-endemic

We therefore have the equation,

$$\text{degree of endemicity} = a \times b \times d$$

It will thus be seen why the disease is endemic in hot damp tropical climates and in coastal areas where an even temperature is the rule, why it is seen at its best in densely populated areas, especially in towns in which the Culex population is not controlled, and why there is considerable variation in the intensity of the endemicity from place to place within these areas The more practical importance of this appreciation of the factors concerned in transmission will be its application to prevention (*vide infra*)

PATHOLOGY

As in other filarial diseases, the pathological changes are caused by the adult and pre-adult worms passing through or lodging in the tissues and giving rise to local reactions in these tissues, the circulating microfilariae themselves apparently produce no recognizable tissue reaction

Morbid anatomy

There is evidence of tissue irritation from the point of entry of the mature larvae onwards The skin around where the larvae penetrate may become thickened, hard and red, and this condition usually persists for some days The

[5] Temperature and humidity are the main factors in determining the complete development of the filarial embryo in the mosquito so that transmission may take place, a relative humidity of 90 per cent and a temperature between 80° and 90° F appear to be the most favourable (*vide supra*)

lymphatic channels through which the larvae migrate show signs of irritation, apparently as a result of the action of some substance secreted by the larvae The tissues respond by hypertrophy of the endothelial cells of the vessel walls

When the immature worm reaches a lymph node, it must work its way through the lymph spaces between the trabeculae and the lymphoid nodules of the cortex to reach the medulla During this passage considerable local reaction is caused, when numerous mature larvae constantly pass through a node, the whole node increases in size and in the course of a short time it is converted into a mass of eosinophilic granulation tissue and no longer contains any lymphoid tissue As the lymph channels are obstructed by this granulation tissue, lymph can no longer percolate through the node, nor can the larvae pass through it, they are held up distally to the obstruction and there complete their development In some instances, adult worms fail to mate and the sterile female, after living in the lymphatics for some time, and causing periodic reactions, eventually dies and is absorbed or calcified In other instances, the adult worms mate and the female parturates, in this sub-optimal environment With the discharge of the embryos, the uterine fluid—which is expelled at the same time—acting as a toxin, causes lymphangitis and/or lymphadenitis (Insections of tissue containing worms, a large number of desquamated endothelial cells derived from the endothelial lining of the vessel walls can sometimes be seen at the site of the vulval orifice of the worm, which is close to the head end) In this way an obstruction is gradually formed to the centripetal flow of the lymph and the pressure rises in the obstructed lymph channels

The gravid female gives birth to living embryos intermittently, probably for a few days in each month, and this is the most likely explanation for the periodicity of the febrile attacks and other allergic signs and symptoms, both local and general When the gravid female ceases to produce embryos, toxins are no longer excreted to the same extent as during fecundation and for the time being the inflammation subsides

The primary factor in the mechanical production of lymphvarices is this intermittent rise and fall of the lymph pressure Clinically, such varices are seen most frequently in lymphatics that are supported by loose tissue, such as those around the superficial lymph nodes, on the inner aspect of the arm, etc , or, when the deeper lymphatics are involved, the abdominal plexuses and those of the spermatic cord (*vide infra*)

The local reaction to the presence of a foreign body in a lymphatic vessel or in a lymph node may be such that the mature worm, or even the immature worm, is strangled, or such worms may die of old age or for some other reason When this occurs there is an infiltration of lymphocytes, plasma cells and eosinophils and the formation of giant cells, which destroy the worm Meanwhile new blood vessels are formed in the granulation tissue, fibroblasts appear, and eventually the remains of the worm are encapsulated and may become calcified This process may be associated clinically with a sharp local inflammatory reaction and in some cases with a febrile attack Later, there will always be scar formation which will further interfere with lymph flow in this region

When the lymph flow is thus obstructed in the distal parts of the lymph system, the lymph pressure increases, at first the deeper lymphatic vessels dilate, then those of the subcutaneous tissues, and finally the skin lymphatics Lymph ceases to drain from the tissues and the part becomes progressively more swollen Such tissue is known as blubbery tissue and when one cuts into it the lymph exudes and the tissue collapses

In the course of time the fibroblasts in the blubbery skin multiply and form new fibrous tissue which makes the skin dense and hard—the typical elephantoid skin The fibrous induration extends deep down into the lower layers of the skin as far as the sweat glands, interfering with the lymphatics in that region and producing oedema followed by fibrosis around the sweat glands, which are eventually destroyed, so that the skin in elephantiasis is always harsh and dry In the meantime the surface hypertrophy of the epidermis becomes more and more marked, fissures occur in the ill-developed horny layer and allow micro-organisms to invade the corium. In these very large, warty elephantoid limbs repeated attacks of inflammation, originating at the surface and due to secondary bacterial infection, are extremely common and increase the local hypertrophy

When the obstruction is in the deeper lymphatics, the lymph is dammed back causing lymph varices of the abdominal plexuses and spermatic cord, these may rupture into the peritoneum, kidney, bladder, or tunica vaginalis, causing lymph ascites, lymphuria, lymphocele, or, if the obstruction is proximal to the receptaculum chyli, this will lead to a reflux of chyle into these plexuses and, if they rupture, chylous ascites, chyluria, or chylocele will result

The entrance of more and more mature filariae into these dilated tortuous lymphatics keeps up the irritation of the vessel wall, so that the endothelial cells hypertrophy and form a vascular granulomatous mass which projects into the lumen like a papillomatous growth The slightest trauma is likely to rupture the blood vessels in these papillomatous growths and cause bleeding into the lymph vessel, with the production of haematuria, haematocele, etc

When the back pressure extends to the lacteals, these may dilate and eventually rupture into the intestinal tract this reflux flow of chyle may cause chylous diarrhoea, but a much more serious sequel will be infection of the dilated and damaged lacteals which infection may spread backwards to the larger lymph vessels, so that when they rupture serious septic complications are likely to follow

As long as the lymphatic obstruction is only partial or intermittent, microfilariae will find their way into the blood stream, but, if it is complete, the larvae are confined behind the obstruction in the oedematous and hypertrophic limb and do not appear in the blood stream Hence it is the rule that in cases of chyluria and lymphatic varix of the cord microfilariae are almost always found in the blood, whereas in elephantiasis of the limbs and genitalia they are frequently not found (*vide supra*)

The importance of secondary bacterial infection is a controversial subject Some workers, including Leiper (1924), Acton and Rao (1929), and Grace and

Grace (1931), believe that staphylococcal and streptococcal infection play an important part in all the inflammatory processes of a filarial attack, whereas others question this and believe that most of the milder inflammatory reactions, except those originating in the skin, can be attributed to the irritation of the filarial secretions and of the body of the worm itself and to an allergic response on the part of the host to these (O'Connor, 1932) However, the more serious complications, such as acute funiculitis, peritonitis, and septicaemia, are obviously due to sepsis, which may have been haematogenous in origin, but is more likely to have resulted from direct infection from some hollow viscus into which the varices have ruptured

The variations in the lesions produced

Various explanations have been suggested for the differences in the lesions produced by filarial infections in different individuals, but the following explanation appears to the writer to have most support from his personal experience and from recorded data

If the complication of sepsis is excluded, there are two factors concerned, both of which are variable, namely (a) the tolerance of the subject to filarial metabolites, and (b) the intensity of the infection to which he or she is subjected

The human host will fall into one of the four following categories —

(*i*) *Tolerant individuals subjected to few infected bites* their tissues do not react to the filarial metabolites, so that the migrations of the pre-adult worm and parturition of the adult cause little or no reaction, and no clinical symptoms, but microfilariae will always be found in the blood once the worms reach maturity

(*ii*) *Tolerant individuals subjected to a heavy infection* in course of time mechanical blockage of the lymph nodes may occur causing some static oedema, lymph varix, or both, without necessarily any lymphangitis or febrile reactions

(*iii*) *Intolerant individuals subjected to few infected bites at long intervals* little damage is caused to the distal lymph nodes, since they have time to recover between successive passages of the injected larvae, all of which pass through these nodes to reach the deeper lymph nodes, *e g* the juxta-aortic nodes, but here there is a sharp local reaction which eventually leads to blockage, local lymph varix, and chylocele, chyluria, or both The blockage in this area is not complete, so that microfilariae will be found in the blood It is only when secondary—usually streptococcal—infection occurs that the serious and often fatal acute funiculitis follows

(*iv*) *Intolerant individuals subjected to many infected bites throughout the year* the distal lymph nodes, *e g* the superficial inguinal and epitrochlear, are damaged early and obstruct the passage of filariae which come to maturity and parturate in the lymph nodes of the limbs causing periodic attacks of lymphangitis and fever Soon the lymphatics become completely blocked, with resultant elephantiasis, none or few microfilariae can reach the peripheral blood

There is no reason to believe that tolerance is a fixed quality, and it seems possible that many persons who are at first tolerant in course of time become

intolerant Further, there will be degrees of tolerance just as there will be many grades of subjection to infection, and it is not suggested that these four categories are sharply defined

If, now, one of the possible common septic complications is added such as an infection from the skin surface in elephantiasis or from some hollow viscus into which a lymph or chyle varix has ruptured, or possibly a haematogenous infection from some septic focus, *e g* an apical abscess or bowel focus—or if the latter complication of haemorrhage occurs, it will be seen that a very large variety of clinical manifestations can be accounted for

Blood picture

There is no characteristic blood picture in filariasis With the exception of an inconstant eosinophilia, any of the changes that occur can be attributed to complications

The sternal-puncture count done in a series of 53 cases of filariasis showed about normal percentages for all the blood elements (Napier, Das Gupta, and Rao, 1941), the low percentage of eosinophil myelocytes in cases in which there is an increase in blood eosinophils suggests an extra-medullary origin for the latter

A moderate eosinophilia is common in cases in which there are microfilariae in the nocturnal blood but few or no signs of lymphatic obstruction During an acute attack of filarial lymphangitis, there is never any increase of eosinophils and they are not infrequently absent from the peripheral blood

Microfilariae in the blood

Reference should be made to the paragraphs on microfilarial periodicity and on the correlation between filarial infection and filarial disease, above

We have found fewer microfilariae in the sternal marrow than in the peripheral blood, both during the day and during the might

Urine

There are no characteristic changes in the urine in an ordinary case of filariasis

In chyluria, the urine is typically a milky white, but the colour is not constant, in a doubtful case the urine should be shaken up with ether or chloroform to see if it clears, as it will do if the milkiness is due to fat If there is any doubt, the urine should be examined again one to four hours after a fatty meal In chyluria, as also in lymphuria, the urine will coagulate on account of the presence of fibrinogen If it is set aside, it will separate into three strata, an upper milky stratum, a middle pinkish one in which the clot will be seen, and a lower stratum consisting of cells and debris

Microfilariae will be found in about fifty per cent of the cases, either in the lowest layer or in the clot, or one can demonstrate them by dropping a few threads of cotton-wool into the urine, allowing these to sink to the bottom and then recovering a thread and examining it under the low power of the microscope

The fat content will vary from a trace to just over one per cent, and the albumin from a trace to 0 6 per cent

In lymphuria, there is albumin and many lymphocytes, but, except for the possible presence of clots, the gross appearance of the urine is little changed

In haematochyluria and haematolymphuria there will in addition be red cells and some free haemoglobin

SYMPTOMATOLOGY

Classification

From the description of the pathological processes given above, it will be obvious that the clinical pictures produced may be very varied As has been indicated above, there may be a short-lived skin lesion—redness and induration with some irritation—at the point of entry of the larvae, but this is inconstant and is seldom remembered by the patient it therefore need not be considered in the symptomatology Otherwise, the following classification covers the commonest of the filarial syndromes

A Signs and symptoms may be absent
B Lymphangitis and lymphadenitis
  (i) Uncomplicated
  (ii) Septic, which may subside or lead to
  (iii) Abscess formation
C Elephantiasis
  (i) Uncomplicated
  (ii) Complicated by sepsis
  (iii) Either may involve
    (a) The limbs
    (b) The scrotum, penis or labia
    (c) The mamma
D Lymph varix, superficial or deep
  (i) Uncomplicated
  (ii) Rupturing, and producing a variety of non-septic complications
    (a) Lymphorrhoea, of the groin or scrotum
    (b) Filarial synovitis
    (c) Lymphocele (hydrocele)
    (d) Lymphuria
    (e) Lymph ascites
  (iii) Bleeding, as a result of trauma, and producing
    (a) Haematospermia
    (b) Haematocele
    (c) Haematuria or haematolymphuria
  (iv) Suppurating before or after rupture
E Chyle varix,
  (i) Uncomplicated
  (ii) Rupturing and producing a variety of non-septic complications
    (a) Chylocele
    (b) Chyluria
    (c) Chylous ascites
    (d) Chylous diarrhoea
  (iii) Bleeding may occur as in lymph varix and produce a parallel series of complications
  (iv) Suppurating, before or after rupture
F General symptoms
  (i) Fever

(ii) Allergic manifestations
(a) Skin manifestations, *e g* urticaria
(b) Asthma

A full clinical description of each of the very numerous filarial manifestations classified above would be out of place here, but notes are given below on the commoner ones and on those that seem to require some explanation As far as they are applicable, the paragraph indentifications used above are followed

Incubation period

It is usually stated that microfilariae first appear in the blood about one year after the larvae have been injected by the infecting mosquito, but the time may probably be shorter and is often longer However, this cannot be considered the incubation period of the disease, which is even more variable Some indication of this can be obtained from the age at which persons born in an endemic area first show symptoms In many filarious countries, it is seldom that evidence of lymphatic obstructions appears within fifteen years of the date of arrival in an endemic area, although in such cases there will often be a history of periodic febrile attacks with possibly some lymphangitis for several years However, in highly endemic areas this period is frequently much shorter, and recently, from the South Pacific, cases have been reported in which the incubation period was apparently only three and a half months, lymphangitis of the arm and of the spermatic cord was associated with fever, and the finding of the adult worms but not of microfilariae

A Symptomless[6] *infection*

In most endemic areas the majority of the infections are symptomless and in the areas of low and moderate endemicity they remain so indefinitely However, as fresh infections are super-imposed, on account either of sheer weight of numbers of adult worms or of developing intolerance on the part of the host, some of these subjects will later develop symptoms, and naturally the numbers of such persons will vary in direct proportion to the intensity of the infection to which they are subjected (*vide supra*)

B Lymphangitis and lymphadenitis

(i) *Uncomplicated* Attacks may occur at frequent and often regular intervals, it is commonly noted by patients that the attacks recur always at some particular phase of the moon, or in women at one particular state of the menstrual cycle The whole limb and the glands in particular are very painful, and often a red line can be seen running down the limb, in the upper limb the epitrochlear gland is most commonly involved The skin over the lymphatic vessels is red and

[6] The word 'latent' is avoided here because it is often used as an antonym to 'patent' and these infections are certainly patent to anyone who examines the blood at the appropriate time, further, the word also seems to suggest that at any time the worm or worms causing this infection may suddenly be stirred into activity and the infection may then flare up into a clinically patent one, this probably very seldom occurs

oedematous and the whole limb may be slightly swollen. Painful subcutaneous nodules, fixed to the skin, will also appear in about 10 per cent. of cases. The site of the adult worm may be indicated by a particularly red and tender spot.

The local symptoms are accompanied by a febrile attack, temperature 100° F. to 102° F., with general malaise, headaches and pains all over the body, that usually lasts for two or three days. The local symptoms may subside after four or five days.

Not infrequently the general symptoms appear without any definite localizing symptoms, and conversely local signs may be unaccompanied by fever.

(ii) If sepsis, either haematogenous or otherwise, is added, the local and general symptoms will be of a more severe nature, the whole limb being very swollen and red, and the temperature running up to 104° F. or 105° F. daily for a week or more. When such an attack subsides, the limb seldom returns to its previous diameter.

(iii) A local abscess at the site of the dead worm may be left.

C. Elephantiasis

After the first few attacks of uncomplicated lymphangitis the limb may return to its previous size, but in course of time each attack leads to a slight permanent increase in the size of the limb, and in some cases the increase is insidious and occurs independently of patent attacks of lymphangitis. At first there is ordinary pitting oedema, then the swelling becomes harder and does not pit, later the whole limb becomes massive, brawny, harsh and dry, and folds and/or cracks appear, and finally these become infected with septic organisms and ulceration occurs. These changes take place most commonly in the arms, forearms, and hands (figure 1), legs and feet (figures 2 and 3), scrotum (figure 4), penis (figure 1), and labia (figure 5), and occasionally in the mammae.

The bizarre deformities that filarial infection will produce are well known, they are capitalized in the East by beggars who parade them for the purpose of obtaining alms, and in the West by writers of textbooks who always seek the most extreme examples for decorating their pages. Elephantiasis is simply the effect of lymphatic obstruction and may occur in non-filarial subjects, but no condition produces such effective obstruction as filariasis, and in a filaria endemic area all cases of elephantiasis may be accepted as filarial in origin unless there is strong evidence to the contrary.

D. Lymphocoeles

Varices will occur mainly when [illegible] superficially, or in [illegible] tissue and are therefore relatively unsupported. Lymph varix may be found on the surface of a limb, or in the groin (figure 6), in the spermatic [illegible] the scrotum, or in the deep abdominal lymph [illegible], in the bladder wall, or [illegible] the kidney.

They may be (i) uncomplicated or (ii) the varix may rupture (a) [illegible] in the groin or scrotum producing a chylocele, (b) into a joint, e.g. [illegible] hip causing filarial synovitis, (c) into the tunica causing a hydrocele, (d) into the urinary bladder or the kidney pelvis [illegible] chyluria.

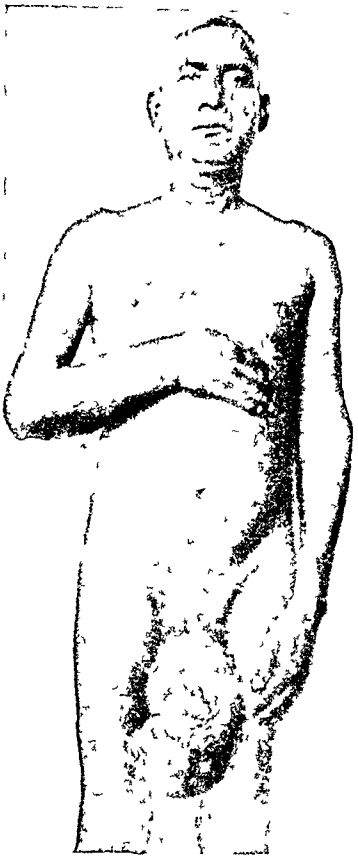

Fig 1 Elephantiasis of Penis, Scrotum, Right Forearm and Hand

Fig 2 Elephantiasis of Scrotum, Penis, Left Thigh, Leg and Foot

Fig 3 Elephantiasis of Left Leg and Foot

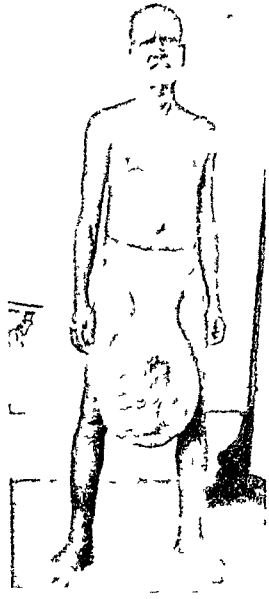

Fig 4 Elephantiasis Scrotum, Prepuce, Right Leg and Foot

(c) Chylous ascites will not be distinguished clinically from ordinary filarial ascites due to the rupture of a lymph varix, but will be apparent when paracentesis is performed, septic complications are more likely to occur than in the simple ascites and in this case the picture will be one of peritonitis

(d) Chylous diarrhoea, resulting from the reflux of chyle into the intestinal canal, has been reported, but is apparently a rare filarial manifestation

(iv) *Suppurating* It will not be necessary to discuss the septic complications that may be associated with any one of these ruptures of chyle varices, but in view of the closer association with the intestinal canal, they are likely to be commoner than in the case of lymph varices, as has been indicated above

F General symptoms

(i) *Fever* The fever that develops in filariasis is due, either (i) to the worm and/or its metabolites, entirely independently of secondary infection, and for this the accepted expression 'filarial fever' is quite appropriate, or (ii) to secondary infection, of the blocked lymphatic channels, of the elephantoid skin, or of the varices, and for this the expression 'secondary fever', to which the words 'of filariasis' might be added if the context did not already make it clear, seems to be unobjectionable [7]

(ii) *Allergic manifestations* Here one is on less certain ground, there is undoubtedly a form of urticaria that is associated with a filarial attack and often recurs at regular intervals, and similarly many filarial subjects with attacks of asthma give a history of periodic attacks that cannot be correlated with the season or with any change in the patient's environment or habits which may or may not be accompanied by local filarial manifestations The writer can give no statistical data in support of this 'clinical impression'

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

This must be considered under a number of headings

(a) *Duration of residence in an endemic area*

The time taken for the development of filarial lesions varies in different localities (*vide supra*), a diagnosis of filariasis at an earlier date should be made with considerable caution, but, as there are exceptions to the general rule, it is also dangerous to rule out filariasis entirely on these grounds alone

(b) *History of a previous attack*

A history of previous attacks of lymphangitis without any apparent local cause, followed by oedema of the limb that does not always subside, and associ-

[7] The fever that occurs when elephantoid skin and tissue become infected has been called 'elephantoid fever' Not only is the expression 'elephantoid fever' an example of a ridiculously misapplied adjective, but it is misleading, as the fever that develops when secondary infection occurs in other filarial conditions, such as lymph or chyle varices, has exactly the same aetiology, and the expression 'elephantoid fever' applied in these cases would be even more ridiculous

ated with a mild or severe febrile attack, should arouse great suspicion Periodic febrile attacks alone in cases in which malaria can be excluded are also suggestive

(c) *Clinical picture*

The acute painful descending lymphangitis and lymphadenitis with fever should always be viewed with suspicion in an endemic area, but they may have other causes, the lymph varix, brawny oedema and elephantiasis of the limbs genitalia or breasts will be more characteristic, but are only evidence of lymphatic, obstruction—the most common cause of which in the endemic areas is, of course filariasis—and not *per se* of filariasis itself, and certain other lesions that commonly occur in filariasis, such as hydrocele, are as likely to have some other cause, even in endemic areas

When hypertrophy occurs in other regions where there is a good collateral lymph supply, *e g* the head or face, back, or buttock, it will seldom if ever be due to filariasis, and such conditions as diffuse fibromatosis, fibro-lipoma and von Recklinghausen's disease should be considered Oedema due to other common causes, such as cardiac and renal diseases, is usually bilateral, but angioneurotic oedema, like filariasis, will usually be unilateral Too much weight should not be placed on the non-pitting character of filarial oedema as it takes some time for the fibrotic changes to occur Hypopituitarism may also produce a condition suggestive of filariasis, but the excess tissue will have a different character as well as being bilateral

(d) *Laboratory examinations*

(i) *Blood* The examination of the blood for microfilariae has its strict limitations as a means of diagnosing filarial disease, *see* p 156, correlation between filarial infection and filarial disease

Summarizing these observations, one can say that the finding of microfilariae indicates filarial infection, but not necessarily filarial disease, failure to find them does not exclude either filarial infection or filarial disease

In countries where the infection is transmitted by *Culex fatigans*, or other night-biting mosquitoes, and the microfilariae show nocturnal periodicity, the blood for examination must be taken between 10 o'clock at night and 2 o'clock in the morning, whereas in other countries, such as Fiji, where it is transmitted by a diurnal biter, the blood should be taken at about 10 o'clock in the morning

Technique Take about 20 cmm of blood, preferably an accurately measured quantity, into a haemoglobinometer pipette, from the finger or ear, and make a thick film on a perfectly clean slide Allow it to dry, then stain and dehaemoglobinize with dilute Giemsa's stain Pour off the stain very carefully—do not wash it off Dry the film in air and examine with a low power lens The number of microfilariae will vary from one in many films to hundreds in one film by multiplying the number per thick smear by 50, the number per ccm will be arrived at

It will sometimes be worth employing a concentration method Take 5 ccm of blood from a vein with a serum syringe into a centrifuge tube containing 10 ccm of distilled water, mix thoroughly until the blood is laked, place two or three threads of cotton wool in the centrifuge tube, centrifuge for 5 minutes with a hand or an electric centrifuge, pour off the super-

natant fluid, pick up the threads with a *rough* straight piece of wire, and examine the sediment with the low-power objective Microfilaria, if present, will be seen entangled in the cotton threads

No assistance will be obtained from the blood count Eosinophilia, though frequently present, is too inconstant a finding to be of either positive or negative value

(ii) *Immunological tests* A complement fixation test in which the antigen is prepared from the dog filaria, *Dirofilaria immitis*, has proved successful but apparently is dependent on the worm being alive

The simpler intradermal test has been used more widely, but there is considerable variation in the technique used A 1 in 8000 *Dirofilaria* antigen with 0 3 per cent phenol, of which 0 01 ccm is given by means of a tuberculin syringe, gives a minimum of false positive reactions, even in allergic individuals A weal of at least 1 ccm in diameter will indicate a positive reaction A H Hamilton (personal communication), basing his opinion on experience in the East Indies, considers that positive intra-dermal tests with dirofilaria antigen are of little value, since about two out of three normal natives will show positive results A negative test however he considers to be of the greatest value as excluding filarial infection

These intradermal tests, for which a really satisfactory standard technique has still to be found, indicate rather the reactivity of the host than the presence of the worms Their particular usefulness will not be in a highly endemic area, but to diagnose an obscure lymphangitis in a patient who has at one time been in an endemic area but shows no microfilariae in the blood A flocculation test with hydrocele fluid has a limited usefulness

(iii) *Urine* The milky urine in chyluria can be identified with the naked eye For this method of examination for filaria *see* p 171 above

(*e*) *Other procedures*

These include cystoscopy and pyelography to identify the sites of the ruptured lymph varices in chyluria, roentgenography to show the presence of calcified filariae, and gland biopsy to identify the adult worm

PREVENTION

This must be considered under two headings· A The prevention of the spread of infection, and B the prevention of attacks in those already infected

A Prevention of the spread of infection

The reader should refer back to p 157 where the essentials for transmission and the factors concerned in endemicity are discussed These are.

(i) The source of infection, microfilariae in the peripheral blood of man
(ii) The vector mosquito
(iii) Susceptible man
(iv) The links between (i) and (ii), and (ii) and (iii).

This aspect of prevention can be discussed shortly under each of these four headings

(i) Man is the only source of microfilariae, but in highly endemic areas a very large percentage of the community will have them in their blood Further, there is no drug that has more than a very temporary effect on the microfilariae in the blood Therefore, any attempt at wholesale 'sterilization' of infected individuals is at present out of the question

Segregation of infected communities should as far as possible be practised This may be advisable when labour forces, police, or armies are recruited from endemic areas, and are to be employed in areas where transmission is possible

Again, the circumstances might be such that it would be advisable to weed out altogether those who had microfilariae in their blood If this were decided upon, it would be advisable to examine several night-blood specimens from each individual

In endemic areas, the highest infection rate is amongst the poorer classes of people who have made no attempt to protect themselves from mosquito bites, so that the uninfected should build their houses well away from poor-class dwellings and should see that any servants that are allowed to sleep in their houses are free from blood-microfilariae

(ii) Control of the transmitting mosquito will provide the most promising line of attack While at least a dozen species belonging to four genera, *Culex*, *Aëdes*, *Taeniorhynchus*, and *Anopheles*, have been found infected in nature and many others have been infected experimentally, *Culex fatigans* is the predominant transmitter in India and in many other tropical countries It is a night-feeder, a breeder in dirty and stagnant water, and comparatively local in its habits, it is not therefore very difficult to control around dwellings by the usual measures directed against either larvae or adults When it is ascertained that some other species is the main transmitter in any locality, special measures must be directed against that species The subject of mosquito control is beyond the scope of this article

(iii) There is nothing to be said under this heading as there is little evidence that there is any individual immunity to infection, and there is certainly no evidence that it is possible to induce or increase such immunity

(iv) In institutions, or even in households, infected persons must be kept in mosquito-proof rooms, or at least under mosquito nets at night, in order to prevent infection of the local mosquitoes

Conversely, for personal protection in mosquito-ridden endemic areas, screening, mosquito nets, suitable clothing, and repellents should always be used, as a precaution against being bitten by infected mosquitoes

B *The prevention of attacks in those already infected*

The most important measure is the removal of any septic focus that might, through the blood, give rise to infection at the site of a dead worm, or in tissue otherwise damaged by filarial metabolites This may be an external one, *e g* a tinea infection or dermatitis, or an internal one, *e g*, pyorrhoea, an apical abscess,

septic tonsils, sinuses, gall-bladder, cervix, prostate, or urinary tract, or a bowel lesion, such as chronic amoebiasis or a *Shigella* infection Elimination of such a focus, *e g* of a subclinical amoebic infection by a course of carbarsone or diodoquin, will often reduce appreciably the number of febrile attacks that a patient suffers

This precaution should be taken in all infected persons whether they have suffered previous attacks or not

However, as well as by removing septic foci, persons who have already had attacks of filarial lymphangitis or some other filarial syndrome can reduce considerably the chances of further attacks by maintaining good general health and, if possible, moving to a cooler climate A recommendation to this effect usually can be made with a clear conscience, as, even if such persons have microfilariae in their blood and there are *Culex fatigans* or other vectors in the locality, they will not be a source of danger to the new community amongst whom they go to live, provided the temperature and humidity are outside the ranges within which transmission occurs (*vide supra*) It is, however, quite unnecessary to recommend such a measure as transfer to a cold climate for an infected person who has suffered no clinical attacks, except of course as a means of preventing further infection

TREATMENT

Introduction

The treatment of this condition is more unsatisfactory than that of almost any other tropical disease, but partly because of this and also because of the variety of the clinical conditions that occur in filarial infection, a very great deal has been written on it It is proposed to treat the subject summarily here It can best be considered under the following headings

A Specific treatment
B Treatment of secondary infections
C The relief of lymphatic obstruction
D Palliative treatment for special conditions

A Specific treatment

No true specific has yet been found, but there does not seem to be any valid reason why at some future date one should not be expected Some drugs when given intravenously appear to destroy the microfilariae, but this does nothing towards helping the patient, for the adult worm, which is not in the blood stream, is left intact When the adult worm has once settled in the tissues, it is difficult to reach it The best method would be to inject some drug that is absorbed by the lymphatics, distally to the worm, so that it would get behind it, so to speak, or, in the case of chyluria and other syndromes following chyle varix, a drug that would be absorbed from the intestinal tract into the lacteals It has been suggested that it would be dangerous to destroy all the worms *in situ* at one time, it might certainly cause a sharp reaction in heavily infected cases, but, should we find such a drug, it would probably not be very difficult to temper the treatment to the heavily infected

Antimonyl tartrates were used by Rogers in 1917, but it was shown that these compounds had no effect on the microfilariae, although they had certain beneficial results on the pathological lesions produced by the parasite Various other drugs have been suggested from time to time The Filariasis Commission of the London School of Tropical Medicine, working in British Guiana in 1921, experimented with many preparations but without success Systematic clinical experiments with various drugs have been carried out by Rao at the Calcutta School of Tropical Medicine, during the last twenty years Patients at various stages of the infection were treated by drugs whose therapeutic efficiency in other parasitic infection was known The results may be briefly stated

Of the organo-metallic compounds, soamin (atoxyl) appears to be most satisfactory in controlling the symptoms in the early stages It can be given subcutaneously, intramuscularly, or intravenously, and is usually non-toxic, although a few exceptionally susceptible persons, who exhibit toxic symptoms even after the first injection, have been encountered There does not appear to be any appreciable reduction in microfilaria-count, even after a full course of treatment with this drug, but in many cases the patients have remained free from fever and lymphangitis for a long time after treatment with soamin Certain other arsenic compounds, such as tryparsamide, novarsenobillon and sulfarsenol, have given almost as satisfactory results as soamin, tryparsamide, given in 2 to 3 gramme doses, intravenously, appeared to control the symptoms in chyluria in particular

Practically all available organic compounds containing antimony were investigated Of these the trivalent compound Fouadin gave the most satisfactory results The drug can be administered subcutaneously, intramuscularly, or intravenously and is non-toxic The effect of the drug on the filarial parasite seems to be temporary, as the microfilariae reappear in the blood after the lapse of some days, though it may be several weeks before they reach their previous level This drug usually controls the inflammation and fever for a considerable time

A recent addition to the antimony drugs used in this disease is anthiomaline—lithium antimony thiomalate Some workers have claimed good results in reducing the microfilaria counts, for several months at least It is given intramuscularly in doses of 2 ccm to 4 ccm of a 6 per cent solution, according to the patient's tolerance, on alternate days, up to 10 doses

Several vegetable drugs which are reported to be efficacious in allied helminthic infections were administered orally and in some cases by injection Oil of chenopodium appeared to give satisfactory results in some cases, when given intramuscularly, it reduced the number of embryos in the circulation and controlled the attacks of lymphangitis, but the injections caused painful reactions

B Treatment of secondary infections

This should be considered under the headings

(i) Local treatment
(ii) General chemotherapeutic treatment
(iii) Vaccine treatment
(iv) The search for and eradication of septic foci

(i) *Local treatment* will naturally depend largely on the part affected and the nature of the lesions Ulcers on an elephantoid leg will in some cases be benefitted by elevation of the limb, followed by the application of powdered sulphonamide to the ulcerated area and tight strapping of the whole affected part of the limb with elastoplast or some similar material which must be left for several days

For lymphangitis and lymphadenitis, whether there is secondary infection or not, hot fomentations and local application of heat by the infra-red lamp will relieve the pain and reduce the inflammation

(ii) Of the *general chemotherapeutic* agents, the new 'sulpha' drugs have proved very useful in the treatment of secondary infections of all kinds and very satisfactory results have been obtained in the treatment of such very serious conditions as epididymo-orchitis and funiculitis by the administration of red prontosil, sulphapyridine and sulphathiazole have also proved very effective, but it is probable that new and more effective anti-streptococcal drugs, *e g*, penicillin, will be in general use shortly

(iii) *Vaccines* have been the mainstay in the treatment of many filarial lesions for some time, and it seems doubtful if the good effects claimed, and in some cases undoubtedly produced, can be attributed to the specific action of the vaccines on the secondary infection The effect has probably been that of non-specific protein therapy in many cases This has obviously been the line of thought of some workers who have used typhoid vaccines or milk injections

A vaccine, consisting of 10 million haemolytic streptococci of many strains and 50 million staphylococci of several strains of *aureus* and *albus*, has been used by Rao at the Calcutta School of Tropical Medicine over a period of 15 years in more than 50,000 cases The vaccine is given intracutaneously in doses of 0 02 to 0 1 ccm twice weekly up to a total of 15 to 20 injections The ameliorative effects have been sufficiently encouraging for him to consider that, in the absence of a specific, this is the best treatment to give, even when there is no evidence of secondary infection Other workers have used autogenous vaccines, and claim satisfactory results

(iv) The *septic focus* that gives rise to the haematogenous infections should be sought and removed (*see* above p 173)

C The relief of lymphatic obstruction

Attendance to the general health of the patient is important, and very often if the patient is sent away to a place with a more bracing climate, there will be some reduction in the size of the limb and therefore presumably an improvement in lymphatic drainage

During an attack of lymphangitis the obstruction is temporarily increased by the inflammation and oedema, and the speed with which the permanent fibrotic obstruction develops will depend to a large extent on how long this is allowed to persist, so that rapid relief is important This is helped by rest, elevation of the limb, and, if it is not too tender, firm bandaging with an elastic bandage Vaccine and non-specific protein treatment are also useful in this capacity

For relief in the quiescent stage, surgeons have devised innumerable operations

for the re-establishment of lymphatic drainage, with little evidence of success Better results are obtained even at this state by bandaging the limb tightly Several forms of permanent bandage have been devised, some are made of elastic webbing and others of more rigid material, such as muslin or even canvas, but fitted with zip fasteners at the top and bottom, so that the pressure can be regulated and released when necessary By this means support is given to the distal lymph vessels and drainage through collateral lymph channels is encouraged, massage and exercise aid this

D Palliative measures

Very often the first demand on the attending physician will be for the treatment of the acute lymphangitic attack and this subject has not been specifically covered above Rest, elevation of the limb, hot fomentations, infra-red rays or even short-wave diathermy applied locally, followed by soothing applications, such as lead or calamine lotions, should be the immediate local treatment, with aspirin and phenacetin by mouth, if this is insufficient, it will be justifiable to give morphia, but it should seldom be necessary to repeat this A brisk saline purgative, a light diet, rest and the continuance of the local treatment, and perhaps a sleeping draught for the next few nights will be sufficient to help the patient through an uncomplicated attack, but, if there is any evidence or even any suggestion of there being secondary infection, it will be as well to give sulphonamides and possibly the other treatment recommended for secondary infection (*vide supra*)

In certain cases, in order to relieve the pressure—and therefore the pain—during an acute attack, small skin incisions have been made with a very sharp knife and a local anaesthetic under aseptic conditions, through these, lymph drains and relieves the tension, but the procedure is not to be recommended as permanent sinuses may remain and these are not only troublesome to the patient but may later become infected

The inconvenience and discomfort of massive elephantiasis of a limb will sometimes be relieved by Auchincloss' operation, or some modification of it In this operation, two parallel skin incisions joined at each end by a V-shaped incision are made in the long diameter of the limb, a wedge-shaped piece of skin and blubbery tissue is removed, the skin under-cut on each side and then drawn together, and the wound closed If possible painful spots, from which the patient may indicate that the attacks usually start, are included in the wedges removed Some temporary relief from the reduction in the diameter and tension in the limb is often achieved by this procedure Amputation is seldom if ever a justifiable expedient

Large scrotal swellings have frequently been removed by operation very successfully As these swellings may reach a weight of one, or even two, hundred pounds, their removal is a very great relief to the patient This also applies to elephantiasis of the mamma and vulva, but, if operation is undertaken, nothing short of complete removal should be attempted

Chyluria should be treated by complete rest, the elimination of all fat from the

diet, and saline aperients If there are clots in the bladder, this may have to be washed out with warm boric lotion of 2 per cent sodium citrate in normal saline Silver nitrate, 1 in 2000 solution, is also recommended as a bladder wash, it has some styptic action When cystoscopy shows that the leakage is in the bladder and is very limited, fulguration has been used, but its application is very limited

PROGNOSIS

Filariasis is not a fatal infection and the expectation of life of the filarial subject is not materially decreased There are a few of the rarer complications of obstruction of the deep lymphatics, such as acute funiculitis which usually leads to peritonitis, that are very fatal, but they occur in a very small percentage of the persons attacked Again, in cases of extensive elephantiasis, ulceration and sepsis may cause exhaustion and eventually death

Many filarial subjects attain a considerable age, and it has even been suggested that the enforced inactivity which the disease may entail actually tends to lengthen the expectation of life

Acknowledgment The writer obtained much of his interest in and personal experience of filariasis through his personal association during the past twenty years with Dr S Sundara Rao, filariasis research worker at the Calcutta School of Tropical Medicine He has referred to Dr Rao's annual reports very frequently while preparing this paper Further, his special thanks are due to Dr Rao for most of the photographs from which the illustrations have been prepared and for his notes on the history of the disease, its distribution in India, and the morphology of the parasite, from which the writer has quoted freely

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MENINGEAL AND VASCULAR SYPHILIS OF THE SPINAL CORD

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The presentation of this material is prompted by the comparative scarcity in the medical literature of authoritative accounts of spinal syphilis One form of syphilitic spinal cord disease, viz , tabes dorsalis, is well known to practitioners of neurology and syphilology, but the less common forms of spinal syphilis are poorly understood In this review we shall attempt a simple exposition of the syndromes produced by syphilis of the meninges and blood vessels of the spinal cord, and of the neurological principles required for an understanding of them Wherever possible illustrative case material is appended

The classification submitted below is based on pathological changes and is useful for purposes of simplified objective description It makes no pretense to finality and may have to be modified as the pathology of these morbid states is further elucidated

A *Syphilitic meningomyelitis* which includes Amyotropic Meningomyelitis (Martin), Syphilitic Spastic Paraplegia (Erb), Amyotrophic Syphilitic Myelitis (Levi), and Systematized Spinal Scleroses (Wilson)

B *Spinal vascular syphilis* (Singer)

C *Syphilitic spinal pachymeningitis*

1 Gumma of spinal cord

2 Syphilitic hypertrophic pachymeningitis (Joffroy and Charcot)

D *Syphilitic poliomyelitis* (Gowers)

Many of the above terms were invented in pre-Wassermann days and have been perpetuated although pathological confirmation of some of them is still lacking The first group, *Meningomyelitis*, is the most common and best known form of spinal syphilis and manifests itself by sensory loss, bladder and leg paralysis and muscle atrophy Each possible combination of these symptoms has, at some time, been described as a separate disease but since all have a common pathological substratum, we have chosen to classify them together The second group, *syphilitic spinal thrombosis*, often called acute transverse syphilitic myelitis, is a well known form of spinal syphilis and requires no further explanation *Syphilitic spinal pachymeningitis* is an inflammation, either intense and focalized (gumma) or moderate and diffuse (hyperplastic pachymeningitis), in and round the spinal dura In classifying both these morbid conditions under one rubric, we support the supposition that they are but variants of the same pathological process Either may lead to spinal cord compression, to occlusion of spinal arteries and secondary necrosis and cavitation, and to degeneration of ventral and dorsal roots of the affected cord segments Concerning the last subdivision, *syphilitic poliomyelitis*, there are widely divergent opinions True it is that localized muscle atrophy may occur in tabetic neurosyphilis (tabetic amyotrophy), meningomyelitis (amyotrophic meningomyelitis), spinal vascular

syphilis and syphilitic hypertrophic spinal pachymeningitis but it is doubtful whether a chronic syphilitic poliomyelitis, similar to the progressive muscular atrophy of Aran-Duchenne exists as a separate entity

HISTORY

Clear distinctions between diseases of the vertebral column and spinal cord were not appreciated before the middle of the last century Then followed an era when all affections of the spinal cord were classed under the epithet "myelitis" With the gradual separation of such clinical and pathological entities as multiple sclerosis by Cruveilhier, tabes dorsalis by Romberg and Duchenne and syringomyelia by Gull, it was learned that syphilis was the cause of a fairly large percentage of the remaining spinal cord syndromes

Descriptions of spinal symptom complexes by many of the great clinicians of the nineteenth century preceded by many years the pathologic study of these same conditions Graves (1) in 1848 described a case of progressive muscular atrophy due to syphilis in his "Clinical Lectures on the Practice of Medicine" The patient had suffered a slowly progressive wasting of the muscles of the right hand and arm By the administration of mercury the progress of the disease was halted and was therefore attributed to syphilis Gowers (2) was also aware that muscular atrophy could succeed syphilis when no other cause was traceable Since then Dana (3), Marie and Levi (4), Mackay and Hall (5), Spiller (21) and many others have written on this topic

Leyden (6) in 1874 reported cases presenting the clinical picture of acute syphilitic myelitis By 1896 Orlofsky (14) was able to collect over 50 cases from the literature and to these he added 20 cases from his own Moscow clinic thus forming one of the largest series and most critical analyses up to that time Gowers (2), Singer (7), Cole (8), and Chung (9) have reported many other cases and their writings are recommended to those students who wish to study the details of this condition

Erb (10) in 1892 described a form of spastic paraplegia which he attributed to syphilis Though lacking pathologic corroboration by even a single case, he and his pupil Kuh asserted that the disease was a primary sclerosis of the lateral and posterior columns particularly in the thoracic segments of the cord The clinical features consisted of a gradual development of spastic paralysis of the lower extremities and bladder and "sensory disturbances that were either slight, severe or absent" Oppenheim (11), and Leyden (6) later expressed the opinion that Erb's symptom-complex may occur in either syphilitic or non-syphilitic spinal cord diseases and that in the latter it could represent any one of several disease processes such as amyotrophic lateral sclerosis, familial spastic paraplegia, etc Other clinical variants which we now recognize as syphilitic meningomyelitis were described by French, German and English writers Petrén (12) reported 34 cases of Brown-Sequard syndrome among them several due to spinal neurosyphilis Nonne (13) and Oppenheim (11), Tooth and Hinds-Howell (15) have recorded cases in which both tabes dorsalis and various forms of syphilitic meningomyelitis were present thus producing a combined postero-lateral sclerosis

Charcot (16) in 1871 and Joffroy (17) in 1873 described a condition still generally known as hypertrophic cervical pachymeningitis in which cervical pains, paresthesia, blunting of sensation and atrophy of muscles in hands and arms were followed by spastic paraplegia and sphincteric disorder Rhein (22), in 1908, was able to collect 35 cases of syphilitic hypertrophic pachymeningitis with secondary syringomyelia from the literature It is improbable that all of these cases would meet the modern criteria required for the diagnosis of neurosyphilis

Contributions to the pathology of spinal syphilis have hardly kept pace with the clinical descriptions Though Virchow and Rokitansky were familiar with inflammation of the soft spinal meninges and the formation of gummata in the spinal meninges and cord, it remained for Bastian (18) to first point out that thrombotic occlusion of spinal arteries was the cause of acute myelitis Singer (7) in 1902 studied, pathologically, two such cases and concluded that Heubner's type of endarteritis, thrombosis of spinal arteries and myelomalacia was by far the most common antecedent of acute syphilitic myelitis The researches of Raymond (19) in 1891, Wilson (20) in 1911, Spiller (21) in 1912, Martin (23) in 1925 have all contributed importantly to our understanding of the basic pathology of these clinical variants of syphilitic meningomyelitis

ANATOMICAL AND PHYSIOLOGICAL CONSIDERATIONS

The special characteristics of spinal syphilis and the many diverse syndromes depend on certain anatomical peculiarities of the spinal cord A few basic anatomical and physiological facts are required for an understanding of these clinical neurological symptoms For further details standard textbooks of anatomy and physiology should be consulted

The spinal cord is a cylinder of nervous tissue which extends from the foramen magnum to the level of the 1st lumbar vertebra and is composed of 31 segments It functions as a conducting mechanism and as a center for certain reflex somatic and visceral activities On cross section the cord is found to consist of white matter or myelinated nerve fibers on the outside and gray matter or nerve cells in the form of an H on the inside These peripherally placed nerve fibers of the white matter conduct sensory impulses which finally reach the cerebellum or cerebrum and motor impulses from cerebrum and brain stem to cells in the anterior and lateral horns of the spinal cord These fibers are divided into tracts, the most important of which are

Ascending tracts	
Tracts of Goll and Burdach	Uncrossed primary sensory neurones conveying impulses for proprioception, vibration, and light touch to nuclei in the medulla whence the impulses are relayed to the thalamus or cerebellum
Lateral spinothalamic tract	Crossed tract for conduction of thermal and pain impulses to the thalamus
Ventral spinothalamic tract	Crossed tract conducting sensory impulses for light touch to the thalamus
Dorsal and ventral spinocerebellar tracts	Uncrossed and crossed tracts which mediate impulses for unconscious proprioception to the cerebellum

Descending tracts	
Corticospinal tract	Fibers from the cerebral cortex which decussate in medulla and provide voluntary control of segmental motor neurones
Vestibulospinal tract	Which conducts impulses from the vestibular nuclei to segmental motor neurones subserving postural adjustments
Reticulospinal tracts	A heterogeneous group of fibers connecting various brain stem nuclei to segmental neurones

Each segment of the spinal cord receives (afferent) a dorsal sensory root composed of the axones of the spinal ganglion cells and gives off (efferent) a ventral motor root, the axones of cell bodies which lie in the anterior and lateral horns of the gray matter Each dorsal and ventral root on one side of a spinal segment

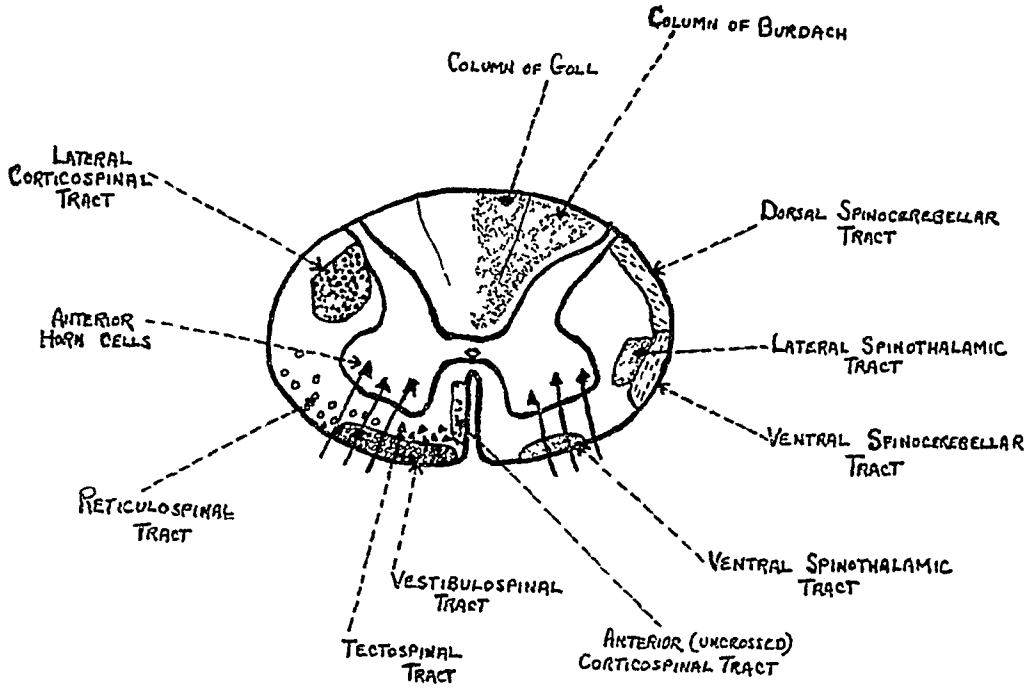

Diagram I Important Ascending and Descending Tracts of Spinal Cord

join to form a spinal nerve Together they form the pathway for the simplest physiological reaction in the nervous system, the segmental reflex

Spinal cord syndromes

The distinguishing characteristics of the multiform symptom complexes depend on the speed, location and extent of the damage to these spinal structures

A Complete transection When the spinal cord is transected by either an inflammatory or vascular lesion, the segments below the lesion are isolated The higher centers of the brain function normally but the patient loses sensibility and voluntary motor control over those parts of the body below the lesion At first the patient is in a condition of "spinal shock", all reflexes are abolished, muscle tone is lacking, and the bladder and rectum are paralyzed After an interval of two or three weeks, unless infection or other factors supervene, this

condition of "spinal shock" disappears The tendon reflexes then become lively but poorly sustained and spinal flexor or withdrawal reflexes, of which the Babinski sign is a fragment, are present Also certain involuntary muscle contractions, often in both the flexor muscles of legs and abdomen, occur whenever a painful stimulus is applied These contractions are termed "flexor spasms" and the tendency for many different muscle groups to contract synchronously results in the so called "mass reflex" Owing to continuous activity of the flexor reflexes the legs may assume a posture of flexion and adduction with formation of contractures Paralysis of legs with a predominating flexor posture is called "paraplegia in flexion," and indicates complete or almost complete cord transection

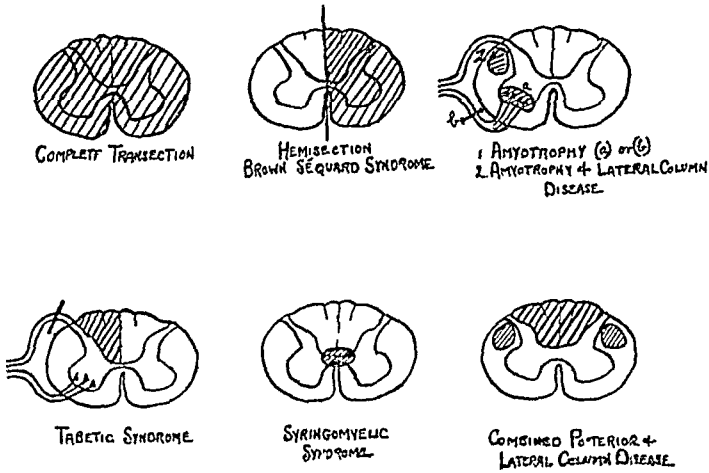

Diagram II Shaded Areas Indicate Site of Lesion

B Incomplete transection If the spinal cord is partially separated from higher centers by a lesion of any type, a state of "spinal shock" identical to the above may develop but with return of reflex activity certain differences from the "spinal man" described above may be noted These differences probably depend on the integrity of the vestibulospinal and reticulospinal tracts which subserve postural adjustments The degree of paralysis and severity of sensory loss will vary with the extent of damage to the corticospinal and sensory tracts, respectively Reflex activity will be heightened and the legs will be spastic Abdominal reflexes will be lost and Babinski signs are present The legs retain a posture of extension due to predominance of the antigravity reflexes The bladder also becomes spastic with limited capacity and involuntary ejection of urine whenever the pressure of fluid within the bladder reaches a certain height (reflex automatic bladder) Paralysis of the legs in a posture of extension is

termed "paraplegia in extension" and probably signifies an incompletely damaged cord In neither this nor the condition of paraplegia in flexion, do the muscles become wasted or atrophic

C Partial injury Partial injury of the spinal cord produces several distinct symptom-complexes depending upon which systems suffer the greatest injury Some of the best known examples are

1 *Brown-Séquard syndrome* which results from section of either the right or left half of the cord Above the level of the hemisection there will, of course, be no clinical signs At the level of the lesion, if several successive segments are damaged, atrophy of muscles, abolition of reflexes and anesthesia will ensue Below the level on the same side as the lesion, there will be motor paralysis of leg and impairment of posterior column sensation (vibration, position sense, proprioception) and on the side opposite to the lesion, loss of pain and temperature sense will occur This crossed sensory disturbance is explained by the decussation of pain and temperature fibers within one or two segments from the level of entry Light touch, which is carried in both the uncrossed posterior columns of Goll and Burdach and in the crossed anterior spinothalamic tract, will not be affected to a detectable degree, nor will bladder function be disturbed

2 *Amyotrophy* If the anterior horn cells are destroyed over several segments of the cord, paralysis, muscle atrophy (amyotrophy) and areflexia will appear . Damage to the ventral roots will produce the same effects The clinical picture would be analogous to that of acute poliomyelitis or progressive muscular atrophy If one or more long ascending or descending tracts are interrupted, signs of corticospinal tract damage or sensory impairment may be conjoined A combination of amyotrophy and pyramidal tract involvement comprises the clinical picture of amyotrophic lateral sclerosis

3 *Tabetic syndrome* Destruction of the posterior or dorsal columns causes sensory ataxia which consists of faulty coordination of muscle movements due to defect of proprioceptive sense, impairment of vibratory sense, astereognosis and areflexia There is usually some degree of cutaneous sensory defect Muscle atrophy and paralysis do not occur This is precisely the state of affairs in tabetic neurosyphilis but such lesions may be produced by other diseases

4 *Combined system disease* Sensory ataxia due to disease of posterior columns and motor paralysis resulting from destruction of corticospinal tracts, comprise the syndrome of ataxic paraplegia This syndrome is most commonly associated with pernicious anemia but may occur in syphilitic meningomyelitis, multiple sclerosis and cord tumor

5 *"Syringomyelic"* syndrome A lesion in the center of the cord which has a vertical extent of several segments may interrupt the decussating pain and temperature fibers The sensory fibers in the posterior columns, which do not decussate, are spared Clinically the lesion will manifest itself by dissociated sensory loss over the affected segments, i e , loss of pain and temperature with preservation of light touch, position sense, vibratory sense This is characteristic of syringomyelia but may be caused by any similarly placed lesion from whatever cause

Circulation The circulation of the spinal cord is by way of one anterior spinal artery and two posterior spinal arteries The anterior spinal artery is formed by a union of a small branch from each vertebral artery and descends in the midline to about the level of 4th or 5th cervical segments Below this point it receives tributaries from the lateral spinal arteries which are branches of the intercostals and lumbar arteries These collaterals, some of which are quite large and others small, enter the spinal canal along the ventral nerve roots and supply most of the thoracic and lumbosacral cord The anterior spinal artery nourishes the anterior two thirds of the spinal cord including the anterior horns of gray matter, the corticospinal and lateral spinothalamic tracts If this vessel is occluded in the cervical region there is a sudden onset of paralysis of all four extremities, bladder and rectum, and loss or impairment of pain and temperature sensation below that level There is atrophic paralysis of arms and hands (anterior horn cell destruction) and spastic paralysis of legs (corticospinal tract damage) Occlusion of this vessel in the thoracic region will produce a similar effect except that the arms are spared If the arterial occlusion is in the lumbar region, the clinical signs will consist of atrophic paraplegia with disturbances of urination, defecation, and impairment of pain and temperature sensation

The posterior spinal arteries also begin from above as branches of the vertebral arteries but descend separately in the posterolateral sulcus They too receive important collaterals from the subclavian, intercostal and lumbar arteries by way of the dorsal nerve roots Being smaller and supplying only a region of the posterior horns of gray matter and posterior columns, occlusion of these vessels produces no dramatic effects

PATHOLOGY OF SPINAL SYPHILIS

A pure form of spinal syphilis without lesions in the brain is exceptional Usually there is pathological evidence of involvement of several portions of the neuraxis

Probably the basic pathologic lesion in spinal syphilis is a chronic inflammation of the spinal meninges, a chronic spinal leptomeningitis Grossly the normal translucency of the arachnoid is altered to an opaque, milky-whiteness which tends to obscure the underlying vessels and surface markings of the spinal cord This membrane is also thickened and attached to the pia by coarse trabeculae These changes are more noticeable over the posterior surface of the cord They may be generalized patchy or diffuse No gross exudate is demonstrable

The microscopic appearance is that of meningeal infiltration consisting entirely of lymphocytes and plasma cells The perivascular or Virchow-Robin space of the more peripherally placed vessels may contain collections of the same cells Depending on the age of the lesion, there will be proliferation of fibroblasts and activation of histiocytes or macrophages

When the meningeal inflammation is acute and of brief duration it may resolve completely leaving no trace of meningeal fibrosis However, when the inflammatory reaction is long continued, there will transpire a degenerative process

which may either damage dorsal roots (? tabetic neurosyphilis) and ventral roots (amyotrophy) or the peripherally placed fibers of the spinal cord (meningomyelitis) If the disease is sufficiently advanced, macroscopic examination will disclose atrophy of dorsal or lateral columns of white matter and a grayness of the white matter that renders it less distinguishable from the central gray matter Then too, either dorsal or ventral roots may be wasted and gray in comparison to the white rounded appearance of unaffected roots

Histological changes vary with the age of the lesion and activity of the process If active, evidence of meningeal inflammation will be found whereas in the inactive stage leptomeningitis is slight or absent

In the acute stage the peripheral portions of the cord adjacent to pia and along the fibrous tissue trabeculae are infiltrated by inflammatory cells and macrophages filled with products of degenerating myelin Nerve fibers disappear and are replaced by fibrous tissue in the roots and neuroglia in the cord This destruction of myelinated nerve fibers may be so slow that the products of myelin disintegration and phagocytosis by histiocytes will not be noticeable

Just how the spinal cord and roots become damaged by a chronic leptomeningitis is difficult to ascertain It is possible that the spirochetes provoke a leptomeningitis and also act on the adjacent tissues This seems, to us, much more reasonable than any such mechanism of retarded spinal fluid circulation as propounded by Hassin (24) Just what relation the arteritic lesions bear to the chronic meningeal process and the parenchymatous degeneration, is not clear In a large number of cases both meningitis and arteritis are found The typical vessel change is exactly the same as that which has been described as "Heubner's Endarteritis" i e, the adventitia and media of the vessel wall are infiltrated with lymphocytes and plasma cells and the subintimal fibroblasts proliferate with narrowing of the lumen of the vessel Whenever these diseased vessels become thrombosed, as not infrequently happens, there will suddenly appear a group of clinical signs and pathologic reactions which are classed as spinal cord infarction or myelomalacia It is usually difficult to locate the thrombosed artery unless at the time the cord is removed, great care is taken to move blood along the meningeal vessels to test their patency The spinal cord in the infarcted region will soften to the point of liquefaction within a few days and after weeks or months a cyst-like cavity will be formed Finally the infarcted region of the cord will exist as a slender, shrivelled structure covered by thickened yellowish membranes The microscopic picture varies with the age of the infarct, which undergoes the same changes as occur in infarcts in the brain The histopathology will differ from that of atherosclerosis with thrombosis and myelomalacia (a very rare condition) only in the degree of lymphocytic and plasma cell infiltration There will be secondary degeneration of ascending and descending tracts

In an intense syphilitic infection of the meninges and spinal cord a gumma may form The pathogenesis of gumma is not known Grossly a gumma of spinal meninges is similar in appearance to one in any other organ It consists of a yellowish, rubbery nodular lesion usually in or around the dura but often com-

pressing or invading cord is well Microscopically it is a granuloma with or without areas of necrosis and comprised of lymphocytes, plasma cells, fibroblasts and histiocytes Langhan's giant cells may be found especially when there has been necrosis Gumma of the spinal meninges may compress or invade the spinal cord with resulting local destruction of tissue and ascending and descending degeneration of fiber tracts (see fig 1) When the inflammation is less intense, the dura may be diffusely infiltrated with lymphocytes, plasma cells leading eventually to a fibrous tissue hyperplasia Here, too, the spinal cord may be

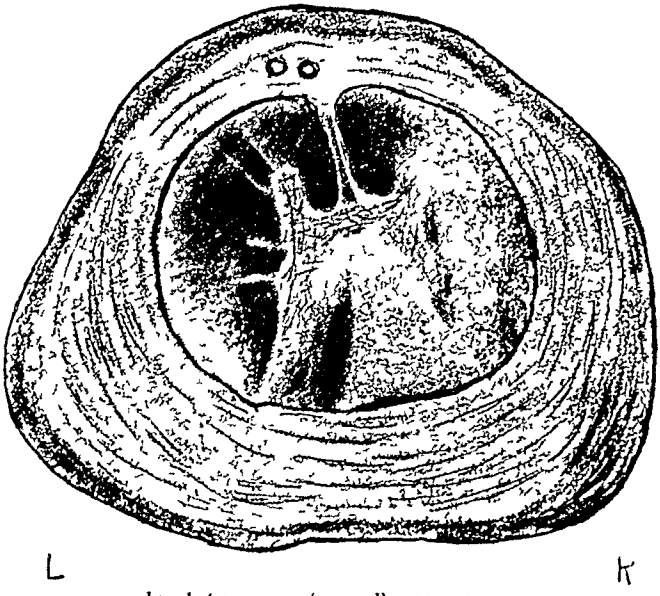

FIG 1 GUMMATOUS SPINAL PACHYMENINGITIS

Note the marked thickening of the meninges and the destruction of myelinated nerve fibers along the margins of the cord and throughout the right posterior and lateral columns (From Nonne Syphilis and Nervensystem Berlin 1909)

damaged by compression or by thrombosis and infarction The end result is a fusiform thickening of the spinal dura and syringomyelia

Syphilis of the vertebral column which secondarily affects the spinal cord is so rare as to hardly deserve discussion Nonne (13) remarked how uncommon it is and quotes Frienkel, a pathologist with great experience in this field, as saying that he had never seen such a case Probably the wide epidural space around the spinal cord, particularly in the dorsolateral regions accounts for this

In summary it should be said that with the combination of chronic meningitis,

arterial disease and granuloma formation, it is not surprising that almost every conceivable cord disease may be simulated clinically by spinal syphilis No one of these pathologic reactions is absolutely pathognomonic of syphilis but taken as a group they are highly characteristic

Frequency of spinal syphilis

Syphilis of the spinal cord is a clinical rarity There were 31 cases of spinal syphilis among 2231 syphilitic patients at the Boston City Hospital This comprises less than one per cent of the total number, an incidence about one tenth that of tabetic neurosyphilis This figure is in agreement with the statistics of Erb, Fournier, Marie and Gerhardt

ANALYSIS OF CLINICAL DATA

The relative frequency of the various types of spinal syphilis, as shown in Table I, is in general agreement with the figures of other investigators

TABLE I

Frequency of various types of spinal syphilis

A Syphilitic meningomyelitis	15 cases
B Spinal vascular syphilis	10 cases
C Syphilitic spinal pachymeningitis	
1 Gumma of spinal cord	3 cases
2 Syphilitic hypertrophic cervical pachymeningitis	1 case
D Syphilitic poliomyelitis	21 case
E Spinal cord compression	
1 Gumma of vertebra	0 cases
2 Aortic aneurysm	1 case

Distribution As in other forms of neurosyphilis this form of the disease occurs preponderantly in males The ratio of men to women in our series was about four to one Our data permit of no general statements regarding racial, occupational, or social group incidence

Age incidence The age at which the clinical symptoms were first manifested varied between 34 and 64 years The majority of the patients were in the fifth decade of life

Latent interval The interval elapsing between the initial syphilitic infection and the first symptoms of spinal syphilis could not always be ascertained because of ignorance of primary infection in many instances This interval varied between a few months and 25 years In general syphilitic spinal thrombosis developed sooner than meningomyelitis, with an average of 6 years for the former as compared to 24 years for the latter The number of the cases is too small for these figures to have any validity

Previous treatment Over two thirds of our patients had received no antisyphilitic treatment and in the remainder the treatment was inadequate according to modern standards

SYMPTOMATOLOGY

The symptoms and signs of the different forms of spinal syphilis are so diverse that any effort at schematization will inevitably fail to include aberrant cases. While the average case is easily recognized, exceptional cases may simulate almost every known spinal cord disease. It is of value to distinguish between spinal cord gumma and pachymeningitis, spinal vascular syphilis and meningomyelitis because of the importance of exact diagnosis in directing treatment and judging prognosis in an individual case. Therefore, each of these types of spinal neurosyphilis will be discussed as separate clinical entities. The reader must remember that these forms often merge or overlap.

Symptomatology of syphilitic meningomyelitis

In a large majority of cases the onset of the disease is so insidious that the patient is unable accurately to date the first symptom. The course is variable; it is usually progressive but may occasionally be punctuated by acute episodes. It may, however, undergo spontaneous arrest but a complete remission, so characteristic of multiple sclerosis, does not occur.

The advent of the illness is most apt to be indicated by weakness or paresthesia of legs. Less often sphincter disturbances mark the onset. In a few cases severe pains over back and encircling the trunk are the first symptoms.

The principal symptoms and signs are paraparesis or paraplegia, urinary and fecal incontinence and sensory disorders consisting of pains, paresthesia and sensory impairment of varying degree. Often the earliest symptom, weakness or stiffness of legs is almost invariable in the later stages of the illness. Both legs are usually involved simultaneously. The patient complains that his legs are tired, stiff, and examination discloses weakness, spasticity, increased tendon jerks and extensor plantar responses. Absent abdominal reflexes and ankle clonus are also present. The gait is slow, stiff, and feet scrape on the ground. As the disease progresses weakness proceeds to almost complete paralysis but, even in late stages, some movement is still possible and legs remain in a position of extension.

The state of the sphincters is nearly always altered sooner or later. Micturition becomes frequent and precipitate. The patient complains of difficulty in starting to urinate, in completely emptying the bladder or in refraining from the act when the occasion is unsuitable. The control of the bowels is similarly though less obviously, affected.

Sensory disorders are the most variable part of the picture. Subjective sensations of the nature of numbness, coldness, tingling are often felt. Girdle sensations consisting of tightness, sense of constriction, may be present. Occasionally severe pains over spine, around the trunk or radiating to the legs are experienced in the beginning or during the course of the illness. Unless tabetic neurosyphilis is conjoined the pains are not of the character of lightning pains or gastric crises. Objective sensory loss is not always easy to demonstrate. Impairment of vibratory and position sense in feet and legs is usually present. Rarely are tactile, thermal or pain sensibility diminished to the same degree. A definite sensory

level is found in only about one third of the cases Due to loss of position sense ataxia may be present so that the gait is one of ataxic paraplegia

When ventral roots are involved by the morbid process, muscle atrophy, loss of tendon reflexes and fascicular twitchings occur In the lower cervical region atrophy of hand muscles develops, if the lumbar segments are the site of the most severe pathologic alteration, similar changes appear in the legs To the total clinical picture thus is added an amyotrophy

At any point in the evolution of the disease mental symptoms or cranial nerve palsies may develop Meningomyelitis may appear in the course of tabetic or paretic neurosyphilis Spinal arteries may become suddenly thrombosed

TABLE II

Symptoms and signs of syphilitic meningomyelitis

Analysis of 15 cases—Neurological Unit—Boston City Hospital

Age 34–64 (average 49 years)		Associated mental symptoms	26%
Sex 12 male, 3 female		Diplopia	6 7%
Primary-secondary syphilis	46 5%	Deafness	6 7%
Latent interval (average 24 years)		Abnormal pupils	46 6%
Previous treatment		Reflex changes	
None	65%	Hyperactive in legs	60%
Inadequate	35%	Absent in legs	20%
Mode of onset and course		Hyperactive in arms	40%
Insidious and progressive	73%	Absent in arms	6 7%
Subacute	14%	Babinski	80%
Acute	13%	Spasticity of legs	10%
Weakness or paralysis		Sensory disturbance	
Legs only	67%	Level—? present in	33%
Arms only	7%	Dimin deep sensation	73%
Legs and arms	20%	Dimin cutaneous sensation	60%
Sphincter disorders		Ataxia—Romberg sign	46 5%
Bladder	60%	Muscle atrophy	
Bowel	20%	Arms	26 6%
Paresthesias	46 5%	Legs	13 4%
Pain	33%	Muscle fasciculations	6 7%

converting the spastic paraparesis to a flaccid paraplegia with urinary retention and anesthesia (spinal vascular neurosyphilis)

Case I Syphilitic meningomyelitis

Gradually developing paraplegia with sensory loss and sphincter incontinence

History The patient, a 52 year old waitress, had been followed in the medical out patient department for several years because of cardiac decompensation which required digitalis and careful cardiac regime Several times it was necessary to admit her to the medical ward because of congestive heart failure For the past 2–3 years she had complained of progressive weakness and numbness of the legs During one hospital admission it was reported that knee jerks and ankle jerks were hyperactive, Babinski signs were present and that she was in-

continent of urine and feces Due to progression of these neurological symptoms she was admitted to the neurological service There was no history of primary syphilis or of antisyphilitic therapy

Examination Patient was obese and complained continuously of pains in back and abdomen She was rational and cooperative There were aortic diastolic and systolic murmurs, cardiac enlargement and wide pulse pressure Walking was almost impossible owing to marked weakness of the legs Pupils were unequal in size, irregular and reacted only slightly to light but well on accommodation and convergence Cranial nerves were otherwise negative The strength of the arms was normal, reflexes were active and there was no sensory loss All muscles of the lower extremity were weak but there was no atrophy Knee jerks and ankle jerks were hyperactive The Babinski sign was present bilaterally There was impairment of all forms of sensation in the legs and lower part of the trunk with an indefinite sensory level at about D-10

Laboratory Urine albumin 1+ Blood Wassermann and Hinton tests positive Cerebrospinal Fluid Pressure 90 mm , dynamics normal, cell count 43, all lymphocytes, protein 228 mgm , Pandy 3+, gold sol 3444544 132, Wassermann and Davies Hinton positive While in the hospital she was digitalized and antisyphilitic treatment (bismuth and mapharsen) was given without any change in her neurological status One week after discharge she re-entered in cardiac failure and died a few hours afterwards

Anatomical diagnoses Syphilitic meningomyelitis Syphilitic aortitis and insufficiency of aortic valve Cardiac Decompensation

At post mortem examination the spinal and cerebral leptomeninges were thickened and milky white in color There was no cerebral atrophy or enlargement of the ventricles A granular ependymitis, most marked on floor of the IV ventricle was noted The thoracic portion of the spinal cord was small but on cut section no definite grayness of the posterior or lateral funiculi could be detected

Microscopic study of spinal cord showed the leptomeninges to be infiltrated with lymphocytes and plasma cells Clusters of these cells had accumulated in the pia and in the sheaths of blood vessels in the periphery of the cord A few of the larger meningeal vessels were infiltrated but the typical changes of Heubner's endarteritis were not seen The myelinated fibers beneath the pia and adjacent to the veins radiating from the periphery of the spinal cord were degenerated and replaced by glia The nerve cells in gray matter had not been affected The changes described above were found in all portions of the cord, and were most severe in the thoracic segments There was no evidence of myelomalacia Ascending and degeneration of nerve fiber tracts could be traced (see figs 2, 3 and 4) There was some lymphocytic infiltration of the meninges of the brain stem The cerebral cortex was normal

Case II Syphilitic meningomyelitis complicated by spinal thrombosis

Gradual onset and progression of paresthesia of legs paraplegia, back pain and incontinence

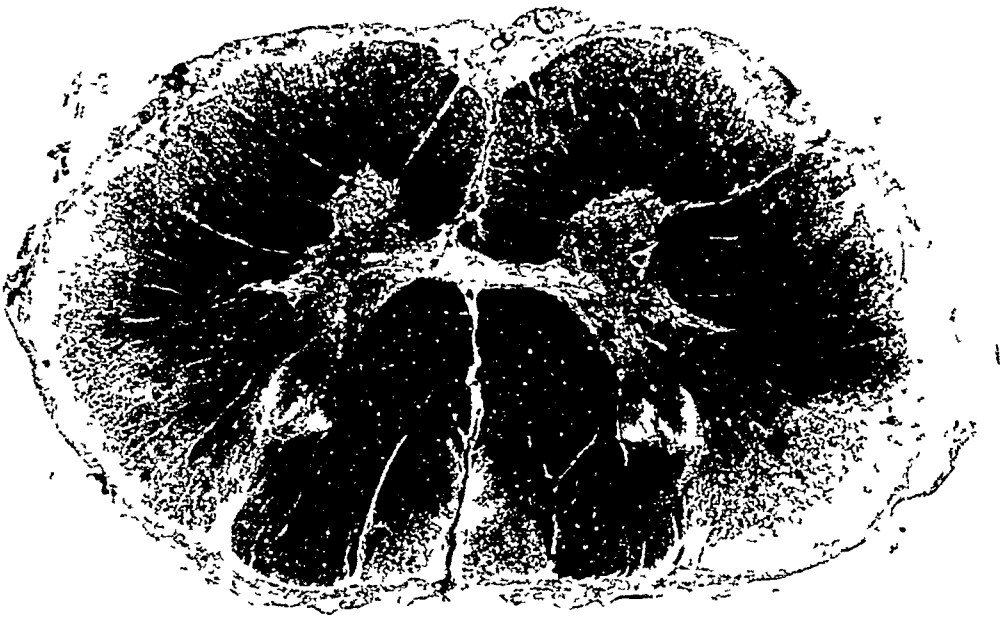

FIG 2 SYPHILITIC MENINGOMYELITIS

The leptomeninges are thickened and the nerve fibers adjacent to them are degenerated Weigert stain

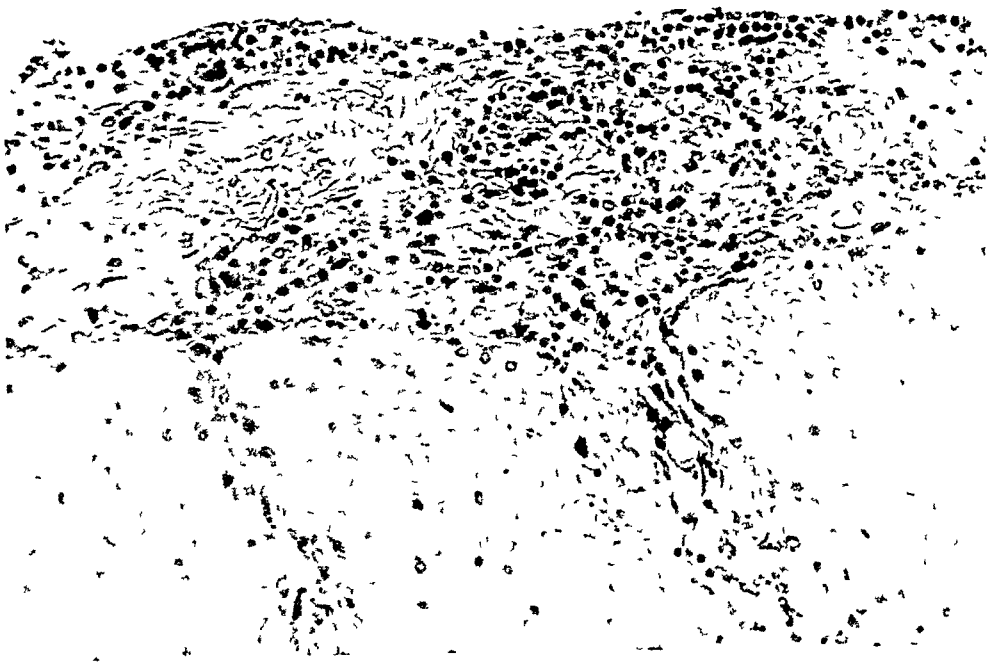

FIG 3 SYPHILITIC MENINGOMYELITIS

The leptomeninges and the fibrous tissue septa are infiltrated with lymphocytes, plasma cells and histiocytes Nissl Stain

History The patient was a white male, 51 years of age whose total illness was of 6 years duration The first symptom was numbness and paresthesias of the left foot and leg followed by paresthesias of the right leg Both legs gradually became weak and stiff and walking was difficult For an indefinite period of time he had had pains and tenderness in the lumbar region and obstinate constipation together with hesitancy and precipitancy of micturition Four months ago while in a local hospital for study, he rather suddenly lost completely the use of his legs He claimed that this developed soon after a lumbar puncture Since then he has been unable to move his legs or control his bladder There was no history of primary syphilis or antisyphilitic treatment

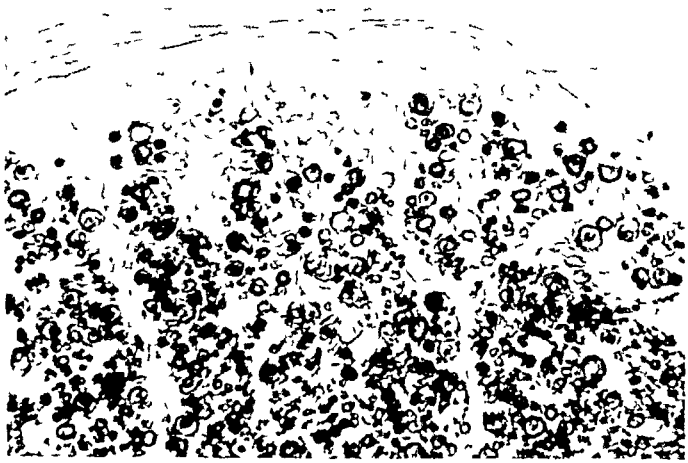

FIG 4 SYPHILITIC MENINGOMYELITIS

Section corresponding to figure 2 to show in a myelin stain, the degeneration of nerve fibers in regions adjacent to the leptomeningitis Weigert Stain

Examination The sensorium was clear The cranial nerves were normal The pupils were small and irregular but reacted to light and on accommodation Strength in the arms was normal There was complete motor paralysis affecting the lower trunk and legs Knee jerks and ankle jerks were not present The plantar responses were extensor in type All forms of sensation were lost below D 8–9 Bladder was distended well above symphysis pubis and rectal sphincter was relaxed There was a decubitus ulcer over both buttocks

Laboratory data Blood Kahn negative Cerebrospinal fluid normal dynamics, 23 lymphocytes per cu mm, protein 81 mgm per cent, Wassermann weakly positive

Course No definite change was observed during his stay in the hospital When last heard from several months later, he was still under the care of his

local physician who was administering bismuth and tryparsamide There had been no change in his neurological status

Comment Though not verified by autopsy one may presume that this man had been suffering from syphilitic meningomyelitis of several years duration The sudden and dramatic onset of flaccid paraplegia, anesthesia and urinary retention signified a syphilitic spinal thrombosis and myelomalacia The lack of recovery would indicate that the cord damage amounted to a transection and would be irreversible regardless of antiluetic therapy

SYMPTOMATOLOGY OF SPINAL VASCULAR SYPHILIS

The term acute syphilitic transverse myelitis is used to designate the clinical symtpoms and signs which are consequent to specific endarteritis and thrombosis of spinal vessels with resulting myelomalacia The well recognized triad of symptoms and signs are 1 Sudden onset of flaccid paralysis of trunk and legs, 2 Anesthesia of the same parts, and 3 Loss of sphincter control This clinical picture is that of a functional and/or anatomical transection of the spinal cord, usually at level of thoracic segments Other lesions which can give a similar clinical picture are acute epidural abscess, epidural carcinomatous metastasis, multiple sclerosis and acute infectious myelitis The syphilitic etiology can usually be established by serological tests The prognosis is grave, very few patients survive for longer than a few months Treatment is ineffectual in restoring lost function but is usually given in an attempt to forestall further vascular thromboses

In our material there were 16 cases which could be included under the heading of spinal vascular syphilis Ten of these cases occurred spontaneously and 6 after some treatment procedure The acute onset of symptoms following an intravenous or intraspinal injection of an arsenical drug has been termed the therapeutic paradox or Herxheimer reaction by some authors In our opinion the Herxheimer reaction, if it ever occurs in the treatment of neurosyphilis, is very rare We have not observed a single proven case True it is that 4 of our 16 cases of spinal artery thrombosis developed after intraspinal injection of serum (3 Swift-Ellis,[1] 1 antimeningococcus) In such we attribute the acute onset of symptoms to thrombosis of already damaged vessels by the irritating effect of foreign material In other cases it may be a chance coincidence as illustrated by its development in one of our cases following an intramuscular injection of bismuth and in another after a lumbar puncture In the latter cases, which were identical clinically with those following Swift-Ellis treatment, there was no reasonable possibility of a Herxheimer reaction One conclusion which we have come to is that the introduction of any foreign substance intrathecally, whether for spinal anesthesia or arsphenamised serum prepared after the method of Swift-Ellis treatment in a patient who already has neurosyphilis, is fraught with considerable danger The added damage of these agents to an already diseased cord may cause serious neurological symptoms

[1] These cases date from an era when Swift-Ellis treatment was in vogue

Acute syphilitic transverse myelitis may occur in a previously well person or in one who already has some other form of neurosyphilis This form of neurosyphilis is less frequent than meningomyelitis, the ratio being 2 to 3 In some cases the two are conjoined The age range in our small series was 39–49, being slightly younger as a group than those with meningomyelitis because of the shorter latent period between initial infection and neurological symptoms Several cases occurred within the first year after the contraction of syphilis, the average was 6 3 years Only one of the cases had received even questionably adequate antisyphilitic treatment during the earlier stages of the disease

In contrast to meningomyelitis and spinal pachymeningitis the onset of symptoms is abrupt Often without warning (premonitory symptoms in only 3 of 10 cases) the patient loses sensation and motor power below a certain level on

TABLE III

Symptoms and signs of syphilitic spinal thrombosis

Analysis of 10 cases—Neurological Unit—Boston City Hospital

Age 39–49 years		Facial palsy	10%
Sex 7 male, 3 female		Deafness	10%
Primary secondary syphilis	50%	Abnormal pupils	50%
Latent interval—6 3 years		Spinal shock	90%
Previous treatment		Reflexes	
None	70%	Absent in legs	90%
Inadequate	30%	Absent in arms	10%
Mode of onset—acute	100%	Legs became spastic	50%
Symptoms		Legs remained flaccid	40%
Paralysis	100%	One extremity involved (flaccid)	10%
Urinary retention	90%	Sensory loss	90%
Paresthesia	20%	Level D 1–6 in	60%
Pains	20%	Trophic ulcers	50%
Mental symptoms	0		

the trunk This level is most apt to be upper thoracic but may be in the cervical or lumbar region When first seen spinal shock is present, i e , tendon reflexes and tone below the level of the lesion are diminished or absent There is at first urinary and fecal retention followed within a few weeks by incontinence and periodic micturition Trophic ulcers usually develop Only about one half of the cases become spastic, some of the others exhibit a paraplegia in flexion indicating almost complete transection of the cord

Three typical cases are presented below

Case III Spinal vascular syphilis, thrombosis of spinal arteries and myelomalacia

History The patient, a 18 year old housewife with no previous knowledge of syphilitic infection, began in January 1941 to have difficulty in micturition About 2 weeks later she awoke in the morning and experienced numbness and weakness of both legs By evening she was completely paralyzed and unable to void urine In the next few days the numbness ascended to level of nipples

Neither the patient nor her husband had noted any change in her mental functions These had been no pregnancies by either this marriage or a previous one

Examination Patient was cooperative, memory good, no dysarthria Pupils were unequal, right was 4 0 mm and left 5 0 mm in diameter, neither one reacted to light but both contracted well on accommodation-convergence The cranial nerves and arms were normal Both legs were completely paralyzed Tendon reflexes were active in arms and absent in legs, abdominal reflexes were absent, plantar reflexes were extensor in type There was loss of all forms of cutaneous sensation below D-8 The bladder was distended and hypotonic and the rectal sphincter was relaxed

Laboratory data Urine normal Blood hemoglobin 85 per cent, white blood count 13,400, Hinton and Wassermann reactions positive Cerebrospinal fluid pressure 95 mm of water, dynamics normal, 360 lymphocytes per cu mm , total protein 206 mgm per cent, colloidal gold was 1223322100, Wassermann strongly positive and Davies-Hinton positive

Course Patient was placed on tidal drainage and sulfathiazole was given for cystitis and decubitus ulcers In the succeeding weeks her legs remained paralyzed and assumed a position of flexion (paraplegia in flexion) Sensory level receded to a lower thoracic level Tendon reflexes in legs returned and strong flexor spasms became increasingly frequent Antisyphilitic treatment consisted of potassium iodide by mouth, intramuscular injections of bismuth and intravenous injections of mapharsen The injections were given every 5 days for a period of 4 months At the end of this time the cells had disappeared from the spinal fluid, the protein content had diminished to 48 mgm per cent, the colloidal gold was unchanged but the Wassermann was less strongly positive The patient was discharged to her home Her bladder care became impossible and she developed cystitis and pyelonephritis which were responsible for her death soon afterwards

Necropsy The spinal meninges were cloudy white and thickened The lower thoracic and lumbar segments of the cord were shrunken and yellowish in color Blood could not be forced into the anterior spinal artery below D-10 The affected portion of the cord was a soft, pulpy mass, much reduced in size In many places it was reduced to small irregularly shaped cavities surrounded and traversed by yellowish-white tissue The ventral and dorsal roots in the thoracic segments were reduced to thin gray, thread-like structures In lower lumbar and sacral segments the roots were normal in size and color (see fig 5) There was slight opacity of the cerebral leptomeninges but no atrophy of frontal convolutions or ventricular enlargement The ependyma of the ventricles was slightly granular

Microscopic examination showed a slight infiltration of the spinal leptomeninges with lymphocytes and plasma cells Many of the spinal arteries were occluded by organized and partly recanalized thrombi and others showed the characteristic picture of hyperplastic (Heubner's) endarteritis The spinal cord in the most affected regions was almost completely destroyed, only a few myelinated fibers in ventral funiculi being preserved (see fig 5) Both myelin-

ated fibers and nerve cells were replaced by macrophages, hypertrophic astrocytes were abundant Ascending degeneration could be traced in the columns of Goll as far as medulla There was no evidence of paretic neurosyphilis

Anatomical diagnoses 1 Meningovascular syphilis of spinal cord with a Endarteritis and thrombosis of anterior and posterior spinal arteries b Myelomalacia 2 Acute cystitis and bilateral pyelonephritis

Comment The acute onset of a flaccid paraplegia with sensory level was indicative of a vascular lesion with complete or almost complete interruption of

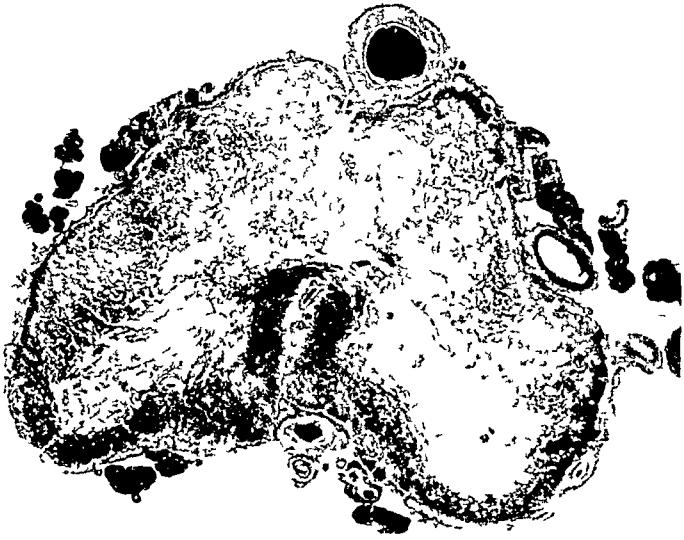

FIG 9 SYPHILITIC SPINAL THROMBOSIS

The anterior spinal artery was occluded at a level above this lumbar segment The posterior and lateral columns and most of the gray matter has been infarcted (Myelomalacia) The topography of the cord is altered Weigert Stain

the continuity of the spinal cord The permanence of paralysis despite antisyphilitic therapy which cleared up the leptomeningitis to a large degree, corroborated this impression The myelomalacia was so marked that even the most intensive therapy could never have restored spinal cord function

Case IV Tabetic neurosyphilis with acute syphilitic spinal thrombosis after Swift-Ellis treatment

History Patient was a white male of 51 years who entered the hospital complaining of sharp, shooting pains in back and chest He had had a chancre 25 years ago and was treated by mercury pills for several months at that time

Examination The patient was mentally sound Positive findings included Argyll Robertson pupils, feeble knee and ankle jerks, positive Romberg, slightly ataxic gait and impaired vibratory and position senses in feet and legs

Laboratory The blood Wassermann reaction was positive The cerebrospinal fluid contained 2 cells and the Wassermann test was strongly positive

Course It was decided to treat the patient by the method of Swift-Ellis which was then in vogue Within a few hours of the first intraspinal injection the patient developed a flaccid paraplegia, bladder paralysis and loss of sensation below the 4th segment Decubitus ulcers and ascending urinary infection resulted and death followed in a few weeks No autopsy was obtained

Comment This case clearly illustrates one of the dangers of intraspinal therapy However, the same pathologic changes could have occurred as well after intraspinal injection of meningococcus serum This type of reaction cannot be considered a therapeutic paradox

Case V Syphilitic meningomyelitis, syphilitic spinal thrombosis following malaria inoculation

History Patient was a 46-year old clerk who had been experiencing numbness and stiffness of the legs for past 6–9 months These symptoms were of insidious onset and gradual progression Recently he had suffered aching pains in back No difficulties in micturition had been noted Ten years before onset of these symptoms he had received several injections in hip and arm for syphilis

Examination The patient was intelligent and cooperative The pupillary reflexes and cranial nerves were normal His gait was spastic and slightly ataxic The tendon reflexes in legs were hyperactive and Babinski sign was present bilaterally The abdominal reflexes were absent and position and vibratory senses were diminished but not lost completely in the legs No sensory level could be detected

Laboratory The blood Wassermann test was positive The cerebrospinal fluid contained no cells, 56 mgm protein per 100 cc the gold sol reaction was 0123322100 and the Wassermann test was positive

Course On the second hospital day 5 cc of blood from a patient with inoculation malaria was injected intravenously On the 6th day his temperature began to rise Coincidently his legs became completely paralyzed, a sensory level at D-12 marked the upper limit of complete anesthesia, urinary retention and paralytic ileus appeared Abdominal distention was so marked that respirations were embarrassed Ileostomy was performed without relief Malarial fever was terminated with quinine but the patient died on the tenth hospital day

Post mortem examination disclosed syphilitic aortitis, insufficient to cause distortion of aortic valve or dilatation of arch of aorta There was syphilitic meningomyelitis and endarteritis with thrombosis and myelomalacia of lower thoracic segments of spinal cord In addition there were similar vessel changes and numerous small infarcts in medulla and cerebrum

Comment In our opinion malarial fever should not have been used in the treatment of this patient It would have been preferable to have administered

neosalvarsan or mapharsen intravenously, together with potassium iodide by mouth and bismuth intramuscularly

Thrombosis of spinal vessels need not always cause a complete transverse myelitis Occasionally only a small portion of the spinal cord may be infarcted in which case the loss of function may be slight Such cases account for the relatively rare Brown-Séquard and syringomyelic syndromes

Case VI Spinal and cerebral meningovascular syphilis incomplete transverse lesion of spinal cord and tabetic neurosyphilis

History The man, aged 49, was a trapeze performer who had noted pains and a sensation of coldness in the legs for several years He had also become im-

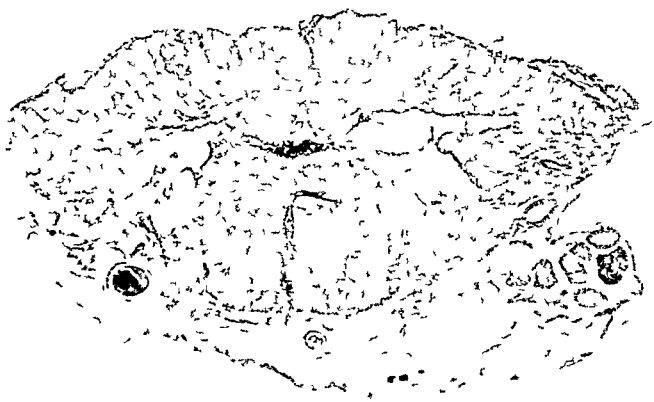

FIG 6 SYPHILITIC SPINAL THROMBOSIS
An artery at the bottom of the field is thrombosed There is infarction with cavitation of gray matter (pseudo syringomyelia) Nissl Stain

potent and less certain of his gait so that he retired from his former occupation Then followed, after an abrupt onset, weakness of both legs and numbness and some difficulty in urination The latter cleared up and strength gradually returned in the succeeding months Psychotic symptoms next appeared leading finally to State Hospital admission

Examination Middle aged man with a depressed facies, impaired memory and visual hallucinations There was a mild left hemiparesis involving chiefly the arm and face Over the lower trunk there was a level below which pain and temperature, and to a lesser extent, light touch, vibratory and position senses

[1] The pathological material from this case was furnished by Dr Louis Goodman of the Howard Hospital, Rhode Island

were impaired The left knee jerk was greater than the right The ankle jerks were absent and Babinski's signs were present on both sides

Laboratory The blood Wassermann test was positive The cerebrospinal fluid was normal except for a protein content of 49 mgms Hinton test was not done

Course The patient was treated by intramuscular injections of bismuth and intravenous injections of tryparsamide at weekly intervals until death three months later from an intercurrent pulmonary infection

Post mortem Syphilitic aortitis Cerebral and spinal meningovascular syphilis Old infarct in right lenticular nucleus and internal capsule, pseudo-syringomyelic cavity in thoracic cord (see fig 6)

SYPHILITIC AMYOTROPHY

Muscular wasting is seldom seen in patients suffering from neurosyphilis It may however be a component of any one of the clinical syndromes itemized below

a Tabetic neurosyphilis with amyotrophy
b Syphilitic meningomyelitis with amyotrophy
c Spinal vascular syphilis with amyotrophy
d Progressive muscular atrophy due to syphilis

A rather small percentage of tabetics, variously estimated at 5–10 per cent develop localized muscular weakness and atrophy sometime during the course of their disease This is usually in lower limbs, e g , unilateral or bilateral foot drop, but occasionally the upper extremity may be involved The pathology of the condition has never been elucidated S A K Wilson (21) from a careful pathologic examination of 2 such cases, discovered degenerative changes in the corresponding anterior horn cells which he attributed to the action of syphilitic toxin He did not find evidence of peripheral neuritis nor of sufficient meningitis to account for the damage of anterior roots

Mention has already been made of localized muscular atrophy especially in hands and arms in cases of syphilitic meningomyelitis Martin (23) designates this condition as amyotrophic meningomyelitis and reported several cases examined both clinically and pathologically The muscle wasting in these cases is best explained by damage of the ventral roots where they pass through inflamed meninges In nearly all of these cases the cervical segments of spinal cord are most intensely affected

Syphilitic endarteritis may cause a small infarct in the ventral horn without involvement of long tracts The case below illustrates this type of syphilitic amyotrophy

Case VII Scapulohumeral muscular atrophy due to syphilitic endarteritis, thrombosis and infarction of anterior horn in cervical spinal cord

History The patient was a Portuguese cook who consulted his physician because of weakness of the left scapulo-humeral muscles of several months duration The onset appeared to have been acute and there was little if any progress during the next few weeks

convergence Vision was acute and the optic fundi were normal The left arm was weak and tendon reflexes were diminished in both left arm and leg There was atrophy of the small muscles of the hand and fascicular twitching of arm and forearm muscles on left side Plantar responses were flexor and the abdominal reflexes were active The gait was uncertain with a tendency to favor the left leg The Romberg test was negative There was no impairment of cutaneous or deep sensation of either the arms or legs Examination of the heart was negative

Laboratory Blood and cerebrospinal fluid serologic tests were negative The cerebrospinal fluid was examined on two occasions and was found to be normal except for the presence of 20 lymphocytes on one occasion

Course During the ensuing 3 months weakness of muscles and wasting progressed to the point where he could no longer move the left leg Tendon reflexes became less active disappearing entirely in left arm and leg Antisyphilitic therapy in form of potassium iodide, bismuth, mercury succinimide and tryparsamide were given Fascicular twitchings of muscles of all four extremities and trunk were observed Finally respiratory muscles became affected, the diaphragm and thorax movements were feeble There were no sphincter disturbances The pulse rate became rapid and the patient died after an illness lasting approximately 6 months

Clinical diagnosis Progressive muscular atrophy, ?syphilitic

Pathological diagnoses Syphilitic aortitis, progressive muscular atrophy—?syphilitic

The principal pathologic changes, aside from the syphilitic aortitis, were found in the spinal cord Extensive disease of the anterior horn cells was found throughout the spinal cord Many of these cells had disappeared completely while others remained in a diseased state as indicated by shrinkage and hyperchromatism Hyperplasia and hypertrophy of astrocytes occurred throughout the ventral horns In the cervical segments the perivascular spaces were filled with lymphocytes and an occasional plasma cell The leptomeninges, however, contained no inflammatory cells In the thoracic and lumbar segments the perivascular infiltrates were absent Ventral roots, motor nerve fibers and muscles were secondarily degenerated The corticospinal tracts were not degenerated There was no trace of syphilitic endarteritis or of meningoencephalitis Giemsa, Gram and Levaditi stains failed to disclose organisms of any kind

Comment The clinical course in this case is entirely consistent with progressive muscular atrophy (Aran Duchenne), a disease of unknown etiology The muscle weakness, atrophy, fascicular twitchings, and tendon reflex loss all signify a progressive degeneration of the lower motor neurones The only clinical finding that could possibly incriminate syphilis as the etiology was the historical fact of primary-secondary infection 30 years before but the completely negative serology tended to exclude this possibility

At post mortem examination, however, there was definite histologic evidence of syphilitic aortitis The changes in the spinal cord differed from those of progressive muscular atrophy only in that there were lymphocytes in perivascu-

lar spaces For this reason, despite the negative blood and cerebrospinal fluid serology, it seems possible that spirochete pallida was the causative agent There is no way of being certain, however, that this case was not one of progressive muscular atrophy in a patient with syphilis and that the lymphocytes were due to the rapidity of the degeneration (often found in infarcts and non-inflammatory conditions)

The failure of mercury, bismuth, potassium iodide and tryparsamide to halt the progress of the disease is of interest Possibly none of these drugs were given for a sufficiently long period of time to be effective

SYPHILITIC SPINAL PACHYMENINGITIS

Syphilitic spinal pachymeningitis was found in 4 of our cases, in 3 there was a gumma and in 1 there was a diffuse inflammation and thickening of the dura, so-called hypertrophic pachymeningitis In the 3 cases with gumma, the clinical picture was suggestive of a rapidly growing tumor Root pains and paresthesia at the site of the gumma, spastic paraplegia, urinary and fecal incontinence with sensory loss below the level of the gumma, comprise the essential details The onset was insidious and the progress of the disease was subacute The possibility of gumma was suggested by the finding of a characteristic spinal fluid alteration, i e, Froin's syndrome (dynamic block, xanthochromia, very high protein 392–924 mgm) and a strongly positive Wassermann test

The other case was representative of the condition known as syphilitic hypertrophic spinal pachymeningitis The earliest symptoms included pains and paresthesias in the arms and hands followed later by atrophic paralysis of the hand and arm muscles, segmental sensory loss and spastic paraplegia The process developed slowly over a period of 18 months The cerebrospinal fluid findings were the same as those in spinal gumma The only clinical distinction between gumma of the dura and hypertrophic pachymeningitis appeared to be the slower evolution and greater tendency to segmental muscle atrophy and sensory loss in the latter

All of the patients with gumma were operated upon after a short trial of antisyphilitic treatment which proved to be ineffective At operation very thick granuloma of meninges was found to be compressing and partly invading the spinal cord Surgical biopsy disclosed characteristic picture of gumma All 3 patients died, one postoperatively, one in 3 months and the third in 9 months In the last case cerebrospinal fluid improved on intensive antiluetic therapy but the clinical condition became worse

Case IX Gumma of spinal cord and meninges Clinical picture of spinal cord compression

History The patient, a 35 year old housewife, first began to experience pain in the low back in February, 1931 A few days later, her right leg became numb and weak The latter condition very gradually increased in severity and, during the third week of the illness, the left leg became similarly affected so that it was impossible for her to walk In addition there was paralysis of bladder function

No history of syphilitic infection or antisyphilitic treatment could be elicited

Examination· There had been no apparent alteration in the patient's intellectual functions Pupillary reflexes were normal The cranial nerves were normal Arms were of good strength and sensation above the 11th thoracic dermatome was normal Below this level there was marked impairment of all sensory modalities Urinary and rectal sphincters were relaxed and could not be voluntarily controlled Skin over buttocks was red and beginning to desquamate The legs could be moved only slightly Tone was diminished and the legs were maintained in a position of extension Tendon reflexes in the arms were normal but were barely elicitable in the legs The Babinski sign was present bilaterally and abdominal reflexes were absent

Laboratory Blood Hinton and Kahn tests were positive Cerebrospinal fluid was under pressure of 150 mm of water and there was complete dynamic block, the fluid was yellow, clotted on standing and contained 24 lymphocytes per cu mm , a total protein of 924 mgm per cent and a colloidal gold of 0000000122 The Wassermann test was positive

Course The patient was treated with neosalvarsan, bismuth and potassium iodide for one month with no improvement It was then decided to do a laminectomy Upon opening the dura a reddish gray tumor mass in the dorsolateral spinal meninges at D-9 level was found and removed This surgical specimen measured 2 5 by 0 8 by 0 8 cm and the pathology report was "gumma of spinal meninges " Following the operation the patient rather suddenly became completely paralyzed with a sharp sensory level at D-9 In the following weeks she improved slightly insofar as some voluntary movement of legs returned and legs became spastic in extension However, she was never again able to walk Transfer to a convalescent home was arranged and neosalvarsan and bismuth injections were continued A few weeks later decubitus ulcers increased in size, the bladder became infected and she died

Comment· The clinical picture evolved much in the manner of a rapidly growing spinal cord tumor Indeed, were it not for the serological reports, this would have been the diagnosis The cerebrospinal fluid findings, together known as Froin's syndrome, established syphilis as the etiology The lack of therapeutic response to neosalvarsan and bismuth has been observed in all the gummas included in our series The sudden postoperative paraplegia was undoubtedly the result of a thrombosis of spinal arteries which did not completely destroy the cord because the legs later became spastic in extension If she had not succumbed to decubitus ulcers and pyelonephritis, one could have anticipated continued improvement for several months

Case X Syphilitic hypertrophic pachymeningitis

History The patient was a negro waiter, 33 years of age, who was admitted to the hospital because of pains in his shoulders and weakness of his legs The pains began 14 months before admission, were of a severe aching character with a tendency to radiate out over both shoulders Some months later his right hand very gradually became weak and atrophic and the left one later became

similarly affected About 6 months before admission, the right leg became weak and stiff During the past few months he had developed frequency and urgency of urination In the two weeks prior to admission he had been incontinent

The patient had had gonorrhoea at the age of 21 but denied having had syphilis

Examination Patient was cooperative and rational on admission Pupils were equal in size, round, and the reflexes were normal There was atrophy and weakness in the muscles of the right hand and forearm and to a lesser degree in the left hand The left deltoid and supraspinatus muscles were atrophic and weak There was impairment of all forms of sensation over his hands and to a lesser degree in his arms Biceps and triceps jerks were absent There was a spastic paraparesis, right greater than the left with hyperactive tendon reflexes, absent abdominal reflexes and bilateral extensor plantar responses Vibration and position sense were impaired in the right leg His neck was stiff and Kernig sign was present

Laboratory data Blood Wassermann and Hinton was positive Cerebrospinal fluid The fluid was slightly xanthochromic and contained 124 lymphocytes per cu mm The total protein was 486 mgm per cent, the Lange reaction was 1122344455, and the Wassermann and Hinton reactions were positive There was no rise in spinal fluid pressure on jugular compression Coughing or abdominal compression produced a prompt rise in pressure

Course An exploratory laminectomy was performed at C 5 to D-2 The spinal dura was very thick and adherent to the underlying leptomeninges The dura was widely incised and left unsutured Following operation the patient was irrational for several days then began to improve On the eighth postoperative day his temperature was 103–104 degrees and bladder urine contained pus He died on the 10th postoperative day

Anatomical diagnoses Syphilitic Pachymeningitis and leptomeningitis, spinal and cerebral vascular syphilis, compression of spinal cord, cystitis, pyelitis and pyelonephritis

The brain was negative except for slight opacity of the leptomeninges and one small softening 1 5 cm in diameter in the right lenticular nucleus and internal capsule

There was a fusiform thickening in the cervical and upper thoracic portions of the spinal cord which was accounted for by fibrous tissue most of which was on the outer surface of the dura If anything the spinal cord was of reduced calibre in the cervical region The ventral and dorsal roots in this region were atrophic and were buried in the thickened meninges Leptomeninges were thickened and opaque and adhered to the dura The dura over highest cervical segments and lumbosacral segments was not thickened

Microscopic section of the affected dura disclosed dense fibrous tissue in which were lymphocytes, plasma cells, giant cells, fibroblasts and histiocytes In places there were many blood vessels, some with thick and others with thin walls Several fragments of bone were seen in the mass The inflammatory reaction involved the inner layers of the dura and to a lesser extent, the pia arachnoid

The spinal cord had lost its normal markings Many of the anterior horn cells were swollen and vacuolated There was a perivascular lymphocytic infiltration in both the white and gray matter Numerous macrophages had replaced degenerated nerve fibers in the right posterior and lateral columns and to a lesser extent the left ones

Comment The atrophic paralysis and sensory loss in the hands, forearms and shoulders were due to ventral and dorsal root damage The swollen, chromatolytic nerve cells in the anterior horns attested to this same process The meningeal irritation was actually due to a syphilitic leptomeningitis and the long tract signs to compression and possibly incomplete infarction of the cervical spinal cord

SPINAL CORD COMPRESSION DUE TO SYPHILIS

This may be caused by syphilis in any one of four ways 1 by gumma of the leptomeninges, 2 by gumma of vertebra with direct pressure on cord, 3 by a large syphilitic aneurysm of descending aorta with erosion and collapse of vertebra, or 4 by syphilitic pachymeningitis which encloses the cord within a firm fibrous tissue sheath

Reference to the meningeal gumma with spinal cord compression has already been made We have never seen a proven case of gumma of the vertebra which caused cord compression One case so diagnosed, proved at autopsy to be a chronic pyogenic granuloma secondary to osteomyelitis of the spine and another was a metastatic epidural carcinoma As already stated, experienced pathologists deny the existence of this entity

The spinal cord may be compressed by an aneurysm or infarcted if its blood supply from intercostal arteries is interrupted Syphilitic aneurysms more often cause the former, dissecting aneurysms due to medial necrosis of aorta of non-syphilitic etiology, may cause the latter

Case XI Syphilitic aneurysm of descending thoracic aorta with erosion of thoracic vertebra, syndrome of spinal cord compression

History The patient was a 51 year old white man whose first complaint in 1931 was pain in the chest of one year's duration This continued until 1933 when he was admitted to the Massachusetts General Hospital because of weakness and numbness of the legs, both beginning two weeks before when he hopped over a puddle of water Lately there had been some precipitancy of micturition The chest pain varied in intensity, usually being worse at night Gait had been ataxic for an indefinite time Thirty years ago he had a chancre on penis His treatment consisted of a few injections of arsphenamine

Examination The patient was cooperative and rational Although there was slight tremulousness of tongue and lips, no evidence of intellectual deterioration was noted Speech was normal The pupils were irregular in shape, unequal in size and reacted very sluggishly to light but well on accommodation-convergence Cranial nerves were not remarkable The arms were normal both as to motor and sensory functions The legs were weak and spastic in extension.

Pain, temperature, vibratory and position sense were all diminished below sensory level of D-6–7 Position sense was impaired to a greater extent in the feet than the legs The gait was ataxic Sphincters were partially incontinent The tendon reflexes were increased in the arms, diminished in the legs and the plantar responses were extensor in type The abdominal reflexes were absent

Heart was enlarged to left and a soft systolic murmur was heard at the apex, the supracardiac area of percusion dullness was 12 0 cm wide There was no aortic diastolic murmur

Laboratory Blood Wassermann was negative but the Hinton test was positive X-rays and fluoroscopic examinations of chest disclosed a huge aneurysm of thoracic aorta which had eroded the 4th and 5th thoracic vertebrae Partial or complete subarachnoid block was demonstrated by several lumbar punctures, fluid was xanthochromic, contained 2 cells and the protein content was 236 mgm per cent The colloidal gold reaction was 0133334443 and the Wassermann reaction was strongly positive Lipiodol injected into the cisterna magna descended to the level of the 4th thoracic vertebra where it was arrested

Course Surgeons advised against either laminectomy or operation on the aneurysm Consequently he was sent to a convalescent home where neosalvarsan, bismuth and tryparsamide were continued The final termination of the illness was not known

Diagnosis Syphilitic aneurysm of the aorta with a Erosion of thoracic vertebrae D-4 and D-5, b Spinal cord compression

Comment The aneurysm had eroded vertebrae so weakening the stability of the spine that a relatively minor trauma caused it to give way The slow progress of the symptoms, the incomplete interruption of the spinal cord tracts, the dynamic and lipiodol evidence of block all attested to cord compression rather than meningomyelitis or thrombosis and myelomalacia as the cause of this syndrome However, the ataxia, rather hypoactive tendon jerks, more severe position and vibratory sense loss in the feet, and positive cerebrospinal fluid, raises the possibility that the patient had had tabetic neurosyphilis for a long time and that the more recent picture of spinal cord compression was superimposed This, unfortunately could not be verified without autopsy Obviously no amount of antisyphilitic treatment would influence the course of the disease

Hypertrophic pachymeningitis is not confined to the cervical portions of spinal cord, being equally common in other positions Although syphilis is the cause of most cases, several other conditions among them epidural granuloma, tuberculosis, trauma and syringomyelia, have been incriminated

BLOOD AND CERFBROSPINAL FLUID IN SPINAL NEUROSYPHILIS

The blood and spinal fluid findings are summarized in table IV

It is to be noted from these tables that in a high percentage of cases blood and cerebrospinal fluid are both abnormal This is particularly true in active cases In old burned out or well treated cases either blood, cerebrospinal fluid or both may be rendered negative In none of our cases were both the cerebrospinal

fluid and blood serology negative except in the one questionable case of chronic syphilitic poliomyelitis This may possibly happen more often than our data would indicate and in such instances the diagnosis may be exceedingly difficult As in other types of neurosyphilis a negative spinal fluid is rarely consistent with clinical progression A markedly elevated cerebrospinal fluid protein and a dynamic block are strongly suggestive of spinal cord gumma though cervical pachymeningitis must be considered as a possibility In all of our cases of gumma of spinal cord the cerebrospinal fluid Wassermann test was strongly positive Tests of cerebrospinal fluid do not distinguish between meningomyelitis and syphilitic spinal thrombosis

TABLE IV

Blood and cerebrospinal fluid changes in spinal syphilis

	MENINGOMYELITIS	SPINAL ARTERY THROMBOSIS	PACHYMENINGITIS AND GUMMA
Blood serology	Positive, 93%	Positive, 88%	Positive, 100%
Cerebrospinal fluid	Normal	Normal	Block, 100%
Dynamics			
Cells	Increased (10–147 mm ^{3}) in 64%	Increased (10–360 mm ^{3}) in 62 5%	Increased (10–110 mm ^{3}) in 66%
Protein	Slightly elevated (40–240 mg) 66%	Slightly elevated (40–228 mg) 60%	Markedly elevated (342–924 mg) 100%
Wassermann and Davies-Hinton	Positive in 86%—in all except old treated or burned out cases	Positive in 88%—in all except old treated or inactive cases	Positive, 100%

DIFFERENTIAL DIAGNOSIS

It is of importance not only to differentiate spinal syphilis from other diseases of the spinal cord but also to identify the type of spinal cord syphilis The latter offers a valuable clue as to prognosis

The chief points by which meningomyelitis and syphilitic spinal thrombosis may be distinguished are by mode of onset, clinical course and severity of cord damage Gumma may resemble meningomyelitis in its clinical manifestations but the dynamic spinal fluid block, with high protein will readily identify the former

The clinical diagnosis of syphilitic meningomyelitis may at times baffle even the most expert especially in those rare cases where neither blood nor cerebrospinal fluid offer a clue The conditions most likely to be confused with it are multiple sclerosis, syringomyelia, alcoholic encephalopathy and neuropathy, subacute combined degeneration and amyotrophic lateral sclerosis One must be continuously on guard against the possibility of a latent syphilitic who quite by chance has developed an unrelated neurological disease Multiple sclerosis and neurosyphilis are alike in often being the cause of widely disseminated lesions throughout the neuraxis Involvement of the spinal cord, brain stem and optic nerves are common to both Cerebellar lesions and signs of cerebellar ataxia

are rare in neurosyphilis The optic nerve involvement in neurosyphilis is slowly progressive to blindness in most cases with constriction of field or central scotomata In multiple sclerosis, so called retrobulbar neuritis is of acute onset with central scotomata rarely affecting both eyes at once, exhibiting marked remissions and rarely progressing to blindness

Syringomyelia may offer difficulty in differential diagnosis unless it is remembered that kyphoscoliosis and segmental, dissociated sensory loss, so characteristic of this disease, are very rare in spinal neurosyphilis Loss of pain and temperature and preservation of touch over one or several dermatomes can be produced only by a central cavitation of considerable vertical extent This may be the result of infarction but is very rare Otherwise both meningomyelitis

TABLE V

Differential diagnosis between types of spinal neurosyphilis

	SYPHILITIC MENINGOMYELITIS	SYPHILITIC SPINAL THROMBOSIS	PACHYMENINGITIS AND GUMMA OF SPINAL CORD
Latency	24 years	6 years	10 years
Onset	Gradual	Abrupt	Gradual
Course	Chronic progression	Stationary or improved	Subacute to chronic
Symptoms	Paresthesias, pain, weakness of legs, incontinence	Sudden paralysis, urinary retention, anesthesia	Paresthesia, pain, weakness, incontinence
Signs	Spastic paraplegia, slight sensory loss, trophic ulcers rare, extension posture	Flaccid paraplegia, anesthesia below level, trophic ulcers—common, flexion posture	Spastic paraplegia, sensory loss below level, trophic ulcers in severe cases
Cerebrospinal fluid	Normal dynamics, clear, pleocytosis, protein sl elevated, midzone gold sol	Normal dynamics clear, pleocytosis, protein sl elevated, midzone gold sol	Dynamic block, xanthochromic with or without cells, protein very high, third zone gold sol

and syringomyelia may exhibit signs of progressive involvement of long sensory and motor tracts with variable atrophy

In hospitals which include a large portion of chronic alcoholics in their population, one is often puzzled by the various neurological syndromes associated with alcoholism and multiple vitamin deficiencies A combination of encephalopathy with the attendant mental aberration, hyperactive tendon reflexes and Babinski signs superimposed upon an alcoholic neuritis, may simulate almost any form of neurosyphilis including paresis, tabes and meningomyelitis Correct diagnosis is possible only by eliciting the dietary and alcoholic history, by recognizing the associated skin and gastrointestinal lesions of vitamin deficiency, by detection of muscle tenderness, pains and paresthesias together with memory loss, confabulation, delirium, etc Needless to say the incidence of syphilis is very high in this group of patients so that it may be necessary to separate the symptoms of the two conditions

Subacute combined degeneration of the spinal cord may appear before pernicious anemia in a small percentage of cases It runs a subacute course beginning with paresthesia of feet and hands and progressing to an ataxic paraplegia The symmetry of the neurological disorder, the sequence of symptoms (always paresthesia before weakness) achlorhydria, the macrocytic anemia, negative serology and response to liver therapy form the basis for this diagnosis

Whether a pure form of amyotrophic lateral sclerosis is ever due to syphilis is a matter of dispute True, some cases of syphilitic meningomyelitis (Erb's spinal paraplegia) may show bilateral pyramidal tract signs but usually bladder disorder is early (late in amyotrophic lateral sclerosis) and there is some sensory loss (none in amyotrophic lateral sclerosis) There were no cases of syphilitic amyotrophic lateral sclerosis or primary lateral sclerosis among our material

The differential diagnosis of syphilitic spinal thrombosis includes other causes of an acute transverse myelitis such as post-infectious encephalomyelitis, acute infectious myelitis, acute epidural abscess or metastatic carcinoma All are alike in producing severe disturbance of spinal cord function with interruption of all tracts at a certain level Evidence of bone destruction and cerebrospinal block is indicative of either metastatic carcinoma or osteomyelitis of vertebra with epidural abscess Acute infectious myelitis may almost exactly simulate neurosyphilis, usually the onset is abrupt, there may be ascending paralysis and sensory loss and pleocytosis of cerebrospinal fluid up to 1000 cells per cubic cmm Serology should afford a basis for distinction Post-infectious encephalomyelitis rarely affects only spinal cord but usually brain stem and cerebrum thus producing convulsions, coma, etc

Pachymeningitis and spinal gumma are apt to be confused only with tumor or spinal tuberculosis The serology should provide the clue for etiologic diagnosis

RESULTS

In general the clinical results in treatment of spinal neurosyphilis are discouraging Extensive spinal cord disease of any type rarely permits long survival Most patients with complete paralysis succumb in a few months to a year, usually of trophic ulcers, septicemia, bronchopneumonia, pulmonary tuberculosis or acute and chronic pyelonephritis

Our follow-up data are too inadequate to be of service in ascertaining the prognosis Usually, if the patient did not succumb within a few weeks he was transferred to a nursing home where follow up was difficult

The uniformly poor results in these cases are tabulated below

Results in treatment of spinal neurosyphilis

	IMPROVED	UNCHANGED	WORSE	DIED
Syphilitic meningomyelitis	4	3	2	2
Syphilitic spinal thrombosis	4	2	1	3
Gumma of spinal cord	0	0	0	3
Hypertrophic pachymeningitis	0	0	0	1

A Specific treatment

Very few of these patients were treated for a sufficiently long period of time to become serologically negative It is our impression that mapharsen and neoarsphenamine with bismuth and potassium iodide will achieve serological negativity In those who survive the spinal cord lesion the antisyphilitic treatment program should be administered in accordance with same principles as those used in treatment of tabetic neurosyphilis After routine treatment of 6–12 months, if cerebrospinal fluid does not improve or become normal, tryparsamide should be given a trial It is doubtful whether malarial therapy is ever indicated except possibly in the hypothetical case with clinical improvement but persistent cerebrospinal fluid abnormalities In such a case the malaria therapy would be indicated to prevent the development of other forms of parenchymatous neurosyphilis It should not be given without due deliberation because of the possibility of further damage to the spinal cord

B General care of paralyzed patient

From the very beginning every effort should be made to forestall the onset of trophic ulcers and bladder infection Scrupulous attention should be given to the skin over bony prominences such as sacrum, hips, and heels Linen should be smooth, the skin should be washed, dried and powdered and contamination by urine or feces avoided The patient should be turned in bed at regular intervals to prevent development of pressure sores Once the skin becomes reddened every effort should be made to protect it Bland antiseptics and dusting powders are advisable, no one having a distinct advantage over another

Rectal and bladder incontinence require special attention The former is best managed by daily enemas of soap and water An indwelling catheter with tidal drainage is one of the most effective methods of preventing distention of the bladder and cystitis but equally good results may be obtained by periodic irrigation with an antiseptic solution and withdrawing urine every 6–12 hours Presence of bacteria and white cells are sufficient indication for sulfonamide drugs

Weak muscles should not be stretched Sandbags should be placed so as to keep feet at right angles Separation of legs and slight flexion at knees affords most comfort Regular passive movements to prevent fixation and contractures should be conducted daily Flexion attitudes and flexor spasms may become so annoying as to require special surgical treatment In these cases anterior rhizotomy as used by Dr Donald Munro, is the recommended procedure Short of this one can only put the patient on his side and remove some of the sources of cutaneous stimulation If improvement occurs, effort towards reeducation of movement, proper splinting, etc are advisable

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HEMOGLOBIN, PLASMA PROTEIN AND CELL PROTEIN—THEIR INTERCHANGE AND CONSTRUCTION IN EMERGENCIES[1]

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Received for publication February 29, 1944

The main theme of this paper is the *dynamic equilibrium* which exists between plasma protein and cell protein—the *protein flow* from cell to plasma or plasma to cell depending upon the conditions of the moment The cell can supply promptly protein to the plasma—e g , fibrinogen coming from the liver cell, the plasma can furnish promptly to the cell its needed protein—e g , plasma protein by vein can supply all the protein rquirements of the body

Various experiments and observations which relate to this theme may now be presented Probably the most important observation is that all nitrogen requirements of the dog can be supplied by dog plasma given by vein This fact has been established by various publications from this laboratory during the past eleven years (1, 3, 8) The dog can be maintained in a positive nitrogen balance, weight balance and a state of health for weeks while receiving by mouth carbohydrate, fat, minerals, and accessories and *plasma protein as plasma by vein* These plasma proteins under these conditions are utilized without significant nitrogen loss as shown in phlorizinized dogs (4)

Table 1 illustrates well the *conservation of nitrogen when plasma is given by vein* —there being a total positive nitrogen balance of 7 6 gm nitrogen in Periods 9 to 18 inclusive In this experiment (1) about 160 cc normal dog plasma (heparinized) was given daily During Periods 5 to 8 inclusive there was clinical *intoxication*, weight loss, a great surplus loss of urinary nitrogen, high urea and ammonia nitrogen, and high creatine Following Period 8 the sugar by mouth was replaced by a Cowgill diet (sucrose, dextrin, lard, butter, bone ash, a salt mixture plus vitamin supplements) This change effected a rapid return to a normal clinical state, a positive nitrogen balance and weight balance During the periods of intoxication (5 to 8 inclusive) there evidently was some tissue injury to account for the great nitrogen surplus in the urine (about 3 times the control amounts) The excess of creatine would point to muscle protein as a source of at least a portion of the surplus urinary nitrogen Evidently the addition of fat, salts, and accessories favors a normal nitrogen metabolism in this type of experiment and brings the body into a normal balance with very considerable conservation of the body protein and a very low urinary nitrogen output Other experiments in this same paper (1) give data on after periods to show that no

[1] We are indebted to Merck & Company, Inc , for a generous supply of amino acids We are indebted to Eli Lilly and Company for aid in conducting this work

[2] Much of this material was presented at the Medical Centennial of the School of Medicine of Western Reserve University on October 27, 1943

hypothetical nitrogen loss follows these periods of large plasma protein intake by vein

No significant *hyperproteinemia* is observed in spite of all these large injections of plasma by vein Furthermore and of great significance is the fact that long continued daily injections of plasma do not change significantly the albumin globulin ratio If albumin only was used for tissue protein supply and maintenance, then we would expect to see the unused globulins pile up in the circulation The fact that no such surplus appears in the blood plasma of these injected dogs would indicate that *all these plasma proteins are useful* in body protein internal metabolism and are used freely in such a way as to maintain a normal balance between the albumin and globulin fractions, at least approximating the ratio found in the normal dog For example, in Table 3, Dog 37-23 was given very

TABLE 1

Plasma protein by vein effects positive nitrogen balance

Dog 34-146—Sugar, Fat, Salts, and Vitamins by Mouth

PERIODS	PLASMA INJECTED TOTAL N	URINARY N	UREA N + NH_3-N	CREATINE N	CIRCULATING PLASMA PROTEIN	WEIGHT
48 hrs	*gm*	*gm*	*per cent*	*mg*	*gm per cent*	*kg*
1		8 73	89 4	129	7 1	15 9
2		7 58	92 0	96		
3		6 37	89 0	26		
4		6 04	89 2	26		14 5
Dog 34-146—Plasma injection begun—sugar by mouth—intoxication						
5	3 66	11 11	88 4	221	7 0	14 4
6	3 59	10 39	90 0	146	7 7	
7	3 44	14 29	90 7	208	7 9	
8	3 37	17 49	88 9	340	8 3	13 0
Plasma injection plus protein-free diet—positive nitrogen balance						
9	4 36	9 62	88 6	219	8 5	
10	4 11	2 89	68 8	28	7 7	
11	2 21	3 70	73 0	26	7 2	
12	4 12	3 47	71 9	13	7 5	13 3
13	4 42	2 61	64 5	16	7 9	
14	4 17	2 22	55 1	24	8 0	
15	2 14	2 01	56 8	14	7 6	13 2
16	4 24	2 34	58 2	21	8 2	
17	4 12	2 34	62 7	19	8 4	
18	2 02	2 36	63 3	10	8 5	
Plasma injection discontinued—protein-free diet continued						
19		2 44	61 0	31		13 0

Period 1—fasting

Periods 2, 3, 4 given 50 gm dextrose daily by mouth

large amounts of dog plasma by vein and no protein by mouth The albumin globulin ratio ranged from 0 9 to 0 7 during the five-week experiment Further work with the electrophoretic technique in such dogs will be of interest

Reserve stores of protein out of which the body can produce *hemoglobin* needed in anemia or *plasma protein* needed in hypoproteinemic dogs are readily demonstrated in reported experiments

Table 2 represents a considerable experience in protein metabolism It is readily shown in anemic dogs that the ceiling of hemoglobin production is about 10 gm per day effected by a large intake of iron salts plus an optimum food protein like liver The ceiling for plasma protein production is less easily attained and cannot be accurately measured over considerable periods The technical difficulties related to plasma depletion are considerable when rapid production of plasma proteins is effected by a high protein diet Frequent and large bleedings daily with return of the washed red cells may disturb the dog's appetite and destroy the usefulness of available veins—therefore renders the experiment incomplete or terminates the experiment short of the standard period of observa-

TABLE 2

Hemoglobin and plasma protein in body circulation and in reserve stores

Regenerative capacity of dog

	CIRCULATING MASS	MAXIMAL REGENERATIVE CAPACITY PER WEEK	RESERVE STORE
	gm	*gm*	*gm*
Hemoglobin	180	50–70	50–200
Plasma protein	30	50–70+	30–100

Dog 10 kilos = 900 cc blood volume = 500 cc plasma volume
20 gm and 6 gm per cent = normal hemoglobin and plasma protein

tion It is our belief that the plasma depleted dog on a liberal protein diet can produce more new plasma protein (70+ gm per week) than can a standardized anemic dog produce hemoglobin (70 gm per week) This means that a dog under favorable conditions can produce a mass of new plasma protein in 3 days equivalent to its total circulating mass of plasma protein—or *in one day* produce enough plasma protein which if remaining in the circulation would raise the plasma protein level from 4 per cent (a danger zone of hypoproteinemia) to 6 per cent (a normal concentration) Intoxication, fever, or unfavorable protein intake will lessen or even obliterate this optimum favorable response

The *protein reserve* (Table 2) depends upon the diet intake during the control period *preceding* the depletion We do not look at this reserve store as finished albumin or globulin within body cells but as *cell protein* which can be mobilized and modified within the cell and contributed to the blood stream as the particular albumin or globulin needed

Among the plasma proteins the most *labile* is the globulin *fibrinogen* Various stimuli can increase or decrease the circulating volume of fibrinogen—liver injury may reduce it below 0 1 per cent and acute infection (pneumonia) or tissue injury

(sterile abscess) can increase fibrinogen levels above 0 9 per cent Diet also may modify fibrinogen levels (2) and these changes may appear within 24–48 hours or less It is well established (5, 7) that fibrinogen is wholly dependent for production upon the normal liver epithelium

The *liver* comes into any discussion of the plasma protein We believe its importance corresponds to its great size and strategically situated as it is that it is the master organ for protein metabolism Most of the blood from spleen, pancreas, and gastro-intestinal tract floods through the organ with a modest additive arterial contribution (hepatic artery) Fibrinogen and prothrombin (10) derive from hepatic epithelium Evidence is accumulating both clinical and experimental to indicate that the albumins come from the liver and probably some or much of the globulins Contributions of globulins from the reticulo endothelium and other cells may be admitted We have the conviction that the great bulk of the protein syntheses within the body goes on in the liver which supplies the energy and the site for the aggregation of amino acids—furthermore that it is at least possible that the liver produces the fundamental proteins for body nutrition and use It is even possible that the fundamental protein for body exchange is albumin and that globulins represent a slight modification of the albumin effected by the liver cell, reticulo endothelial cell, muscle or other body cells

Protein production, utilization and exchange can be studied best in the dog which has been depleted of some of its essential proteins This protein depletion will stimulate production of the needed proteins and one can then study the utilization of various proteins given the dog by mouth, by vein, or subcutaneously The experiments in Tables 3, 4, and 5 are of this nature and the method is simple though there are experimental difficulties Dogs are placed on a low protein or protein free diet containing adequate amounts of fat, carbohydrate, salts and diet accessories Continued bleeding will deplete the body of hemoglobin and plasma proteins as well as the reserve stores of protein material which contribute to hemoglobin and plasma protein fabrication Within 2 or 3 weeks the reserve protein stores are exhausted and the circulating blood will show hemoglobin levels of 6–8 gm per cent (normal 20 gm per cent) and plasma protein levels of 4–5 gm per cent (normal 6–7 gm per cent) This anemic and plasma depleted animal (doubly depleted dog) can now be given various proteins and the new hemoglobin and plasma protein can be removed to maintain the basic levels observed at the start of the experiment The *output of new blood proteins* is a reflection of the use made of the introduced protein and it is obvious that the dog can use almost any protein more or less effectively to manufacture new hemoglobin and plasma protein (9) The use made of the protein and protein digests is of particular interest at this time These experiments measure quantitatively the blood protein production of the dog stimulated to maximal effort by prolonged depletion and lowering of hemoglobin and plasma protein levels in the circulating blood

These doubly depleted dogs on a protein-free diet can produce practically zero new hemoglobin and plasma protein and furthermore,— they are very susceptible

to any type of infection and many types of intoxication They cannot endure this depleted state indefinitely and loss of appetite often terminates an experiment—the duration often being 3 to 5 months Detailed description of the individual clinical histories, methods, and digests are given elsewhere (9)

Table 3 shows clearly that *dog plasma* can supply protein materials out of which the depleted dog can manufacture *new hemoglobin* in considerable quantities When one gives dog plasma by vein to a depleted dog it would not be surprising if the subsequent continued daily bleedings removed most of the introduced plasma protein On the contrary, the new hemoglobin is produced promptly and in large amounts—even in excess of the removed plasma protein

TABLE 3

Production of hemoglobin and plasma protein due to dog plasma and beef serum digest

PERIOD 1 WEEK	WT	PROTEIN INTAKE		PROTEIN OUTPUT				PRODUCTION RATIO PLASMA PROTEIN TO HEMOGLOBIN
		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk	Level	Output per wk	
Dog No 37 23 Whole fresh dog plasma by vein—60% return								
	kg		*gm*	*gm %*	*gm*	*gm %*	*gm*	%
1	16 8	Basal	76	10 1	12 4	4 1	5 4	
2	16 3	Dog plasma	154	8 3	50 0	7 1	33 4	67
3	16 5	Dog plasma	164	7 8	41 1	6 8	31 9	78
4	16 2	Basal	38	7 6	30 5	5 7	22 8	75
5	16 0	Basal	38	7 4	22 6	4 8	15 1	67
Total output net					125		109	87
Dog No 37-23 Beef serum digest KB 2-47 by vein—30% return								
1	16 1	Serum digest	74	7 5	1 6	4 8	0	
2	15 4	Serum digest	117	7 7	45 2	5 1	22 1	51
3	15 5	Serum digest	117	7 7	1 6	4 8	0	
4	14 5	Basal	19	8 8	17 0	4 5	7 2	42
5	14 0	Basal	19	8 8	1 6	4 6	0	
Total output net					77		27	35

It has always seemed to us improbable that the nucleated red cell (a degenerating nucleus) could accept amino acids and accomplish the arduous task of hemoglobin synthesis and fabrication With the demonstration that plasma protein can contribute freely to new hemoglobin production, we may assume that the plasma proteins together with iron gain access to the red cell and are modified by enzymes, perhaps supplemented by nuclear disintegration products, to form abundant new hemoglobin For every 100 gm of plasma protein introduced we find 60 gm new hemoglobin and plasma protein removed In this type of experiment there is little if any urinary nitrogen excess associated with the plasma injection We may assume that the remainder of the introduced protein was used to supply other protein needs of the body

Serum digests (Table 3) like casein or other protein digests do contribute materials out of which the body makes new hemoglobin and plasma protein The ratio in favor of new hemoglobin is 3 to 1, in spite of the fact that this digest is obviously made up of materials perfectly suited to new plasma protein fabrication Compare Table 5 and hemoglobin digests by vein

Table 4 shows that *dog hemoglobin* can furnish materials which supplemented by protein materials already in the body can make abundant *plasma protein* In our first experiments the hemoglobin was given by vein and only small amounts could be administered due to the low renal threshold for hemoglobin The results were not convincing but when hemoglobin was given into the peritoneal

TABLE 4

Production of hemoglobin and plasma protein due to dog and sheep hemoglobin given intraperitoneally

PERIOD 1 WEEK	WT	PROTEIN INTAKE		PROTEIN OUTPUT				PRODUCTION RATIO PLASMA PROTEIN TO HEMOGLOBIN
		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk	Level	Output per wk	
Dog No 35-6 Dog hemoglobin in peritoneum—123% return								
	kg		*gm*	*gm %*	*gm*	*gm %*	*gm*	%
1	15 8	Fast	0	12 0	16 4	5 7	12 2	74
2	16 1	Hb 24 8 gm	33	12 3	44 6	4 9	18 2	41
3	15 8	Hb 31 9 gm	39	9 1	60 2	4 6	23 1	38
4	14 9	Hb 21 5 gm	30	8 8	4 6	4 0	2 6	57
5	14 8	Basal	7	10 2	9 8	4 4	3 8	39
Total output net					102		38	37
Dog No 40-29 Sheep hemoglobin in peritoneum—150% return								
1	10 6	Basal	36	8 1	1 7	4 6	0	
2	10 4	Hb 37 3 gm	36	8 0	45 3	5 2	20 0	44
3	9 7	Hb 14 1 gm	14	8 0	1 8	4 4	0	
4	9 4	Basal	0	9 9	2 0	3 8	0	
Total output net					62		16	26

cavity, large amounts were given without hemoglobinuria and the experiments are decisive More new hemoglobin and plasma protein are removed than protein given and we may assume complete conservation of the injected hemoglobin plus a supplement taken from body protein Abundant new hemoglobin is formed plus the usual amount (one-third) of *new plasma protein* and the plasma protein circulating level is not seriously depleted

Sheep hemoglobin can be used under these conditions but the injection was discontinued after 10 days to avoid any sensitization reaction The reaction to dog and sheep hemoglobin seems to be much alike

Hemoglobin digests (Table 5) are well used when given by vein—digests made

Serum digests (Table 3) like casein or other protein digests do contribute materials out of which the body makes new hemoglobin and plasma protein The ratio in favor of new hemoglobin is 3 to 1, in spite of the fact that this digest is obviously made up of materials perfectly suited to new plasma protein fabrication Compare Table 5 and hemoglobin digests by vein

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		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk	Level	Output per wk	
Dog No 35-6 Dog hemoglobin in peritoneum—123% return								
	kg		*gm*	*gm %*	*gm*	*gm %*	*gm*	%
1	15 8	Fast	0	12 0	16 4	5 7	12 2	74
2	16 1	Hb 24 8 gm	33	12 3	44 6	4 9	18 2	41
3	15 8	Hb 31 9 gm	39	9 1	60 2	4 6	23 1	38
4	14 9	Hb 21 5 gm	30	8 8	4 6	4 0	2 6	57
5	14 8	Basal	7	10 2	9 8	4 4	3 8	39
Total output net					102		38	37
Dog No 40-29 Sheep hemoglobin in peritoneum—150% return								
1	10 6	Basal	36	8 1	1 7	4 6	0	
2	10 4	Hb 37 3 gm	36	8 0	45 3	5 2	20 0	44
3	9 7	Hb 14 1 gm	14	8 0	1 8	4 4	0	
4	9 4	Basal	0	9 9	2 0	3 8	0	
Total output net					62		16	26

cavity, large amounts were given without hemoglobinuria and the experiments are decisive More new hemoglobin and plasma protein are removed than protein given and we may assume complete conservation of the injected hemoglobin plus a supplement taken from body protein Abundant new hemoglobin is formed plus the usual amount (one-third) of *new plasma protein* and the plasma protein circulating level is not seriously depleted

Sheep hemoglobin can be used under these conditions but the injection was discontinued after 10 days to avoid any sensitization reaction The reaction to dog and sheep hemoglobin seems to be much alike.

Hemoglobin digests (Table 5) are well used when given by vein—digests made

Assuming that the body can manufacture these essential proteins with such speed, it is well to supply digests or amino acid mixtures even when plasma must be given for the acute emergency to maintain the circulating volume These digests are effective by vein, subcutaneously, intraperitoneally, or by mouth Infection and intoxication may slow the response and utilization of these digests

The passage of large protein molecules across cell borders must be admitted, however we choose to explain this phenomenon (11) Fibrinogen must escape from the hepatic cells, and plasma proteins, when given by vein to maintain nitrogen equilibrium, must enter various body cells One reason why it is difficult to discuss this topic is the fact that the early work on cell membrane passage

TABLE 7

Production of hemoglobin and plasma protein due to ten amino acids necessary for growth (Rose)

PERIOD 1 WEEK	WT	PROTEIN INTAKE		PROTEIN OUTPUT				PRODUCTION RATIO PLASMA PROTEIN TO HEMOGLOBIN
		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk	Level	Output per wk	
Dog No 40 32 Amino acid mixture Vc daily—23% return								
	kg		gm	gm %	gm	gm %	gm	%
1	13 9	Basal	34	6 8	1 7	4 7	0	
2	13 8	Amino a —oral	177	8 8	18 5	4 8	12 4	67
3	12 9	Amino a —oral	177	7 5	38 0	4 9	19 8	52
4	12 8	Amino a —vein	177	8 8	15 8	1 7	7 7	49
5	12 6	Basal	0	8 8	1 6	3 9	0	
Total output net					89		34	38
Dog No 37-82 Amino acid mixture Vc daily—46% return								
1	12 6	Basal	10	7 7	7 1	4 6	4 3	61
2	11 8	Amino a —oral	117	9 1	16 8	4 8	7 2	43
3	11 1	Amino a —oral	60	9 1	22 4	4 7	12 2	55
4	10 6	Basal	0	8 1	10 5	1 2	3 3	32
5	9 8	Basal	0	9 4	1 9	1 2	0	0
Total output net					64		20	31

was done upon unicellular organisms which are delimited by a tough and obvious membrane The cell border of an active liver cell is a very different thing and certainly allows ready passage of large protein molecules to and fro from cell to blood and the reverse It is at least possible that the liver cell (and other body cells) have boundaries consisting of lipids and proteins including enzymes which could be responsible for this ready passage of protein molecules

Our concept of a large *protein pool* including the circulating plasma proteins and mobile cell proteins emerges from this discussion The contributions to this pool derive largely from the liver and the withdrawal from the pool may concern any body cell needing protein or capable of storing some surplus protein From

in proportions given elsewhere (9, 6) The mixture is effective by mouth or by vein There is no toxicity observed when given rapidly by vein When the protein equivalents of these amino acid mixtures are figured, we note that 100 gm protein equivalent causes the production of 23–46 gm of new hemoglobin and plasma protein

These depleted dogs (anemic and hypoproteinemic) can use whole plasma (plasma protein) to make much new hemoglobin Serum digests are used in the same way to make hemoglobin and plasma protein but not as effectively as is

TABLE 6

Production of hemoglobin and plasma protein due to a casein digest

PERIOD 1 WEEK	WT	PROTEIN INTAKE		PROTEIN OUTPUT				PRODUCTION RATIO PLASMA PROTEIN TO HEMOGLOBIN
		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk	Level	Output per wk	
Dog No 40-155 Casein digest P36092—25% return								
	kg		*gm*	*gm %*	*gm*	*gm %*	*gm*	%
1	15 1	Digest-vein	182	5 1	41 1	6 6	20 0	51
2	14 8	Digest-vein	188	6 9	20 5	6 5	16 7	84
3	14 0	Basal	26	6 8	10 0	6 0	8 2	85
4	13 3	Basal	30	5 9	10 7	5 9	7 4	72
Total output net					62		45	73
1	14 1	Digest-oral	144	6 3	27 5	5 0	17 8	67
2	13 7	Digest-oral	136	6 3	1 3	5 5		
3	13 8	Digest-oral	131	7 7	13 9	5 3	8 1	61
4	13 5	Basal	18	6 2	22 5	4 8	12 2	57
Total output net					73		38	52
Dog No 37-82 Casein digest P36092—44% return								
1	14 9	Digest-vein	188	10 5	62 7	5 1	29 2	49
2	13 7	Digest-vein	181	8 7	38 0	5 5	17 0	47
3	12 7	Basal	20	8 0	28 6	5 5	14 4	
4	12 1	Basal	27	5 7	22 2	5 1	12 2	
Total output net					116		71	61

observed when whole plasma is given Hemoglobin cannot be contributed to the body protein pool except when the red cell is broken up Hemoglobin is then saved, supplemented, and recast into new protein depending upon body needs and much of this rescued hemoglobin or globin may contribute to the building of plasma protein

These experiments have a direct bearing upon clinical problems, such as parenteral administration of protein material adequate for body nutrition Shock and post-operative therapy bring other related problems before the physician

Assuming that the body can manufacture these essential proteins with such speed, it is well to supply digests or amino acid mixtures even when plasma must be given for the acute emergency to maintain the circulating volume These digests are effective by vein, subcutaneously, intraperitoneally, or by mouth Infection and intoxication may slow the response and utilization of these digests

The passage of large protein molecules across cell borders must be admitted, however we choose to explain this phenomenon (11) Fibrinogen must escape from the hepatic cells, and plasma proteins, when given by vein to maintain nitrogen equilibrium, must enter various body cells One reason why it is difficult to discuss this topic is the fact that the early work on cell membrane passage

TABLE 7

Production of hemoglobin and plasma protein due to ten amino acids necessary for growth (Rose)

PERIOD 1 WEEK	WT	PROTEIN INTAKE		PROTEIN OUTPUT				PRODUCTION RATIO PLASMA PROTEIN TO HEMOGLOBIN
		Type	Weekly	Hemoglobin		Plasma protein		
				Level	Output per wk	Level	Output per wk	
Dog No 40 32 Amino acid mixture Vc daily—23% return								
	kg		*gm*	*gm %*	*gm*	*gm %*	*gm*	*%*
1	13 9	Basal	34	6 8	1 7	4 7	0	
2	13 8	Amino a —oral	177	8 8	18 5	4 8	12 4	67
3	12 9	Amino a —oral	177	7 5	38 0	4 9	19 8	52
4	12 8	Amino a —vein	177	8 8	15 8	4 7	7 7	49
5	12 6	Basal	0	8 8	1 6	3 9	0	
Total output net					89		34	38
Dog No 37-82 Amino acid mixture Vc daily—46% return								
1	12 6	Basal	40	7 7	7 1	4 6	4 3	61
2	11 8	Amino a —oral	117	9 1	16 8	4 8	7 2	43
3	11 1	Amino a —oral	60	9 1	22 4	4 7	12 2	55
4	10 6	Basal	0	8 1	10 5	4 2	3 3	32
5	9 8	Basal	0	9 4	1 9	4 2	0	0
Total output net					64		20	31

was done upon unicellular organisms which are delimited by a tough and obvious membrane The cell border of an active liver cell is a very different thing and certainly allows ready passage of large protein molecules to and fro from cell to blood and the reverse It is at least possible that the liver cell (and other body cells) have boundaries consisting of lipids and proteins including enzymes which could be responsible for this ready passage of protein molecules

Our concept of a large *protein pool* including the circulating plasma proteins and mobile cell proteins emerges from this discussion. The contributions to the pool derive largely from the liver and the withdrawal from the pool may occur in any body cell needing protein or capable of storing some surplus protein Ex

this protein pool may be derived hemoglobin, new plasma protein or cell protein. The circulating plasma protein is the medium of exchange and the body is solvent just so long as there is adequate protein supplies for any emergency. When the body becomes insolvent, there may be a foreclosure due to disease, infection, or injury.

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THE PATHOGENESIS OF CUSHING'S SYNDROME

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INTRODUCTION

In 1932, Cushing (1) described a clinical syndrome with the following characteristics (*a*) painful adiposity confined to the face, neck and trunk, (*b*) kyphosis of the upper thoracic spine, (*c*) hypertrichosis of the face, neck and trunk in females, preadolescence in males, (*d*) dusky plethoric appearance of the skin with purplish lineae atrophicae on the abdomen and thighs, (*e*) hypertension, (*f*) variable backaches, abdominal pains and ultimately extreme weakness, (*g*) dryness of the skin with acne and susceptibility to skin infections Other features frequently but less consistently present were hyperglycemia, glycosuria, diminished sugar tolerance, polyphagia, polydypsia, osteoporosis, bronze pigmentation of the skin, cutis marmorata and purpuric ecchymoses

Of the twelve cases reported on by Cushing, three had a small but definite basophil adenoma, two an undifferentiated adenoma and one a questionable adenoma of the hypophysis Two had grossly normal pituitary glands Although aware of the fact that clinically similar syndromes had been found associated with tumors of other endocrine glands particularly the adrenals, Cushing, nevertheless, hypothesized that the primary cause of the disturbance was a basophil adenoma of the hypophysis

It has since been established that basophil adenomas frequently are found unassociated with Cushing's syndrome, and this syndrome is found without associated basophil adenomas Instead, hyperplasia of the adrenal cortex, a benign or malignant tumor of the adrenal cortex, are the more frequent findings Irrefutable proof of the association of the adrenal tumor with the symptom complex is afforded by the demonstration that a striking remission of symptoms may occur following removal of the tumor (Ravid (2), 1942) The entire question of pathogenesis, however, remained confused because of the many typical cases in which no one pathological condition was consistently found

Such a condition was finally established by Crooke (3) (1935) who described in a series of 12 cases, a peculiar hyalinization of the basophil cells of the hypophysis Of his series, in six, there was a basophil adenoma, in three, an adrenal tumor and in three, a thymus tumor From his investigations Crooke concluded that the change in the basophils indicated an altered physiological activity which was fundamentally significant in the pathogenesis of Cushing's syndrome Rasmussen (4) (1936) also noted this hyalinization of the basophil cells in three cases of clinical basophilism in one of which there was a basophilic adenoma, in one, an adrenal tumor, and in the third, neither He has since examined additional cases all of which have shown the change (personal communication)

[1] Recipient of a grant in-aid-of research of the Commonwealth Fund

One other obvious site, namely, the hypothalamus, remained unexplored in the search for a primary seat of disturbance leading to the changes found in Cushing's syndrome For example, it has been shown (Heinbecker and White (5), 1942) that a properly localized lesion involving the hypothalamic nuclei, particularly the paired paraventricular nucleus, invariably gives rise to obesity Associated with this condition, produced experimentally in dogs, there have also been found many of the changes in other organs and tissues which are evident at autopsy in persons dying of basophilism

This report covers an investigation of six cases exhibiting Cushing's syndrome in five of which the hypothalamus was available for study In all these five, well marked hyalinization of basophil cells was found In four, definite changes in the hypothalamic nuclei, particularly the paraventricular nuclei, were noted In none of these four was an adrenal tumor present In the fifth case in which a malignant adrenal tumor was found at autopsy, no hypothalamic lesion was present In the sixth case an adrenal tumor was removed at operation but the brain was not available for study

The conclusion now seems permissible that either an adrenal tumor or hypofunction of the paraventricular hypothalamic nuclei may be primary causes of the basophil degeneration which in turn is the immediate cause of many of the typical findings of Cushing's syndrome Evidence will be presented to suggest that the hypothalamic dysfunction may lead to hyalinization of the basophil cells through an increased effectiveness of the hormone secreted by the adrenal cortex In this way a common pathway for influencing the hypophysis is found for the various primary disturbances which lead to Cushing's syndrome

CASE RECORDS

A brief clinical history of the cases, together with the autopsy or biopsy findings is first given

Case I White, married female, age 33, well until five years before admission to Barnes Hospital when she began to notice increased hair growth on face, blurring of vision an slight ankle edema During her five years of illness she periodically experienced polyphagia and polyuria For two years before admission she suffered from ulcers on her legs Her skin became dry and scaly, she developed stiffness and weakness of her muscles Frontal headaches, drowsiness were present for two years For the past year she did not menstruate During the six months prior to her death her face became full and rounded, her complexion florid In five years her weight increased from 160 to 208 pounds Purple striae appeared over the lower abdomen and thighs Physical examination on admission revealed a patient with an appearance typical of Cushing's syndrome She had hypertension 200/140, a diminished sugar tolerance, basal metabolic rate −22, daily urine output varied from two to five liters, NPN, 35 mg per cent

The patient's chief reason for being in the hospital was to have the ulcerations on her legs treated The ulcers became infected and the infection spread widely beneath the skin and muscles A streptococcal septicemia finally caused her death

The essential autopsy findings were hyalinization of the cytoplasm of the basophil cells of the pituitary, basophilic invasion of the posterior lobe of pituitary, increased pigmentation of the inner zone of the cortex of adrenal, obesity of trunk and face, hirsutism, striae

of skin of abdomen and right thigh, unhealed infected amputation wound of left knee, draining wounds of left shoulder (abscess drained 13 days ago), healed wounds of right lower leg (recurrent ulcers), edema of subcutaneous tissue of right lower leg, ecchymosis with superficial bullae of skin of the left flank, edema and congestion of lungs, congestion of liver, focal fatty degeneration of liver, focal fatty degeneration of kidneys, hyperplasia of spleen, atrophy of pancreas (15 grams), hyperostosis of bones of skull, focal necrosis with intranuclear inclusion bodies in adrenal and liver, simple cyst of the ovary (10 x 10 x 8 cm.). No pituitary adenoma was present.

Serially cut sections 20 and 8 mm. in thickness through the preoptic and hypothalamic regions stained with cresyl violet revealed marked loss and atrophy of the nerve cells in the various nuclei of this region (fig. 1). These changes were particularly striking in the supraoptic and the paraventricular nuclei. The ependymal lining cells of the third ventricle showed a similar atrophy. Round cell infiltration was lacking. While the blood vessels showed intimal thickening and vacuolization of the endothelial lining cells, such changes were not specific for these regions. Sections were taken at random from the thalamus and brain stem and even when they showed vessel changes showed no nuclear atrophy similar to that seen in the hypothalamus.

Case II. White, married female, age 26, who entered the hospital because of general weakness, amenorrhea, aching pains in the joints, increase in the size of face, neck and abdomen and marked cutis marmorata of the thighs and legs of two years' duration. Headache and dizziness had been marked for six months. For five weeks prior to admission she had severe pain in the chest, a cough and fever.

Her illness followed a miscarriage in the third month of pregnancy. In two years her weight increased from 108 to 150 pounds.

Examination in the hospital revealed an appearance typical of Cushing's syndrome. The blood pressure was 210/170, the fasting blood sugar 245 mg. per cent, her sugar tolerance was markedly diminished. Blood cholesterol 392 mg. per cent, the basal metabolism was −4 in spite of a marked pyogenic infection in the chest at the time. X-ray showed marked demineralization of all bones. Occasional, mild polyuria was reported. Shortly before death the patient developed multiple abscess of the skin. Death resulted from the latter, the chest infection and increasing cardiac weakness.

Autopsy revealed partial hyalinization of basophil cells of the pituitary, obesity of the face and trunk, hirsutism, osteoporosis of ribs and vertebrae, hypertrophy and dilatation of the heart, edema of hands, ankles and feet, striae of abdomen, chest and axillae, bilateral abscesses of chest wall, osteomyelitis of ribs and twelfth thoracic vertebrae, serofibrinous pleurisy, right, purulent posterior mediastinitis, multiple abscesses of kidneys and heart, fatty degeneration of liver.

Serial 20 micron sections of the hypothalamic regions of the brain showed patchy loss of cells in the supraoptic, the paraventricular, the posterior hypothalamic and mammillary nuclei. The ependymal cells lining the third ventricle showed slight but definite atrophy. In some areas particularly in the supraoptic and paraventricular nuclei, the cells are more closely packed due to a collapse of the supporting tissue.

Case III. White male, age 12 years, well until 20 months ago when he developed weakness of his back, this progressed during the year until he was unable to walk without crutches. Soon after the onset of the weakness headaches also were noted. Six months prior to admission general malaise became marked. During the past year obesity of neck, face and trunk developed. Purple striae appeared on the abdomen. There was marked cutis marmorata over the legs. In the hospital the patient presented the appearance typical of Cushing's syndrome. The skeleton showed generalized decalcification. A renal calculus was passed into the bladder and removed. The blood pressure on admission was 140/120, basal metabolism −33, urine negative for sugar, fasting blood sugar 72 mg.

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per cent, blood cholesterol, 295 mg per cent Death resulted from weakness and cardiac failure

At autopsy the following findings were recorded partial hyalinization of basophilic cells of the pituitary, adenoma of basophilic cells of pituitary, arteriosclerosis, generalized, arteriolar nephrosclerosis, cardiac hypertrophy and dilatation, congestion of spleen, edema of ankles, obesity of trunk and face, hirsutism, osteoporosis, extreme, kyphosis and scoliosis of thoracic and lumbar vertebrae, atrophy of muscular system, ecchymoses of skin over left knee and left ankle, draining sinus of right knee, hypertrophy and hyperplasia of islands of Langerhans, suppression of secondary spermatogenesis, fat involution of the parathyroids, involution of the thymus, atrophy of the right adrenal, hypertrophy of the left adrenal, internal hydrocephalus, slight

Serially cut 20 micron sections of the preoptic and hypothalamic areas of the brain revealed loss and atrophy of the cells in various nuclei of these areas The loss of cells was particularly marked in the paraventricular nuclei The cells of the supraoptic nuclei relatively were well preserved

Case IV White male, age 53, five feet, eight inches in height, well until 1918 when at the age of 33 he developed thrombophlebitis of the left leg During next four years he had one or two attacks of thrombophlebitis of the left leg each year In 1925 he developed clinical symptoms of duodenal ulcer In 1931 he had an attack of gallstone colic His ulcer symptoms recurred periodically until 1938 His gallbladder symptoms lasted only about eight months In 1935 he again developed recurring attacks of thrombophlebitis in the right leg X-ray examination revealed calcification of arteries of the leg By 1940 marked kyphosis with demineralization of the spine had developed In 1926 a sugar tolerance test revealed a somewhat greater than normal tolerance, another in 1935 was not abnormal By 1940 a well marked diabetic state existed, hypertension, 200/100, also was present Up to 1939 the blood pressure had not been over 130/80 Only moderate obesity was ever noted, his maximum weight was 186 pounds It existed up to the end of 1938 but after that his weight decreased slowly so that at the time of death in 1940 his weight varied from 136 to 166 pounds Patient was plethoric in appearance with prominent eyes He died of progressive cardiac failure

At autopsy the findings were partial hyalinization of basophilic cells of the pituitary, basophilic adenoma (2 mm in diameter) focal hyperplasia of parathyroids, adenoma of parathyroid in superior mediastinum (3 x 3 x 4 cm) generalized osteoporosis, mucoid atrophy of bone marrow, extramedullary hematopoesis in spleen, nodular goiter, hyperplasia of adrenal cortex, arteriosclerosis of arteries, massive caseous tuberculosis of prostate, miliary tubercles in lung, liver and spleen, sclerosing mastoiditis, bilateral, suppurative mastoiditis, left, bronchopneumonia, slight internal hydrocephalus, fibrous thickening of leptomeninges, subarachnoidal hemorrhage

Serially cut 20- and 8 mm sections of the preoptic and hypothalamic nuclei stained with cresyl violet showed definite loss and atrophy of the cells in the hypothalamic nuclei par-

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FIG 1 PHOTOMICROGRAPHS OF VARIOUS AREAS OF HYPOTHALAMUS FROM CASE I, TOGETHER WITH CONTROLS FROM CORRESPONDING AREAS OF A NORMAL BRAIN

A—preoptic area, × 50, normal brain *B*—supraoptic nucleus, × 50, Case I *C*—supraoptic nucleus, × 50, normal brain *D*—supraoptic nucleus, × 50, Case I *F*—paraventricular nucleus, × 45, normal brain *E*—paraventricular nucleus × 45, Case I *G*—caudal division, supraoptic nucleus, ×, 45 normal brain *H*—caudal division, supraoptic nucleus, × 45, Case I *I*—caudal division, supraoptic nucleus, × 13, normal brain *J*—caudal division supraoptic nucleus, × 13, Case I *K*—supraoptic nuclear cells, × 900 from Fig C *L*—supraoptic nuclear cells, × 900, from Fig D *M*—paraventricular nuclear cells, × 900, from Fig L *N*—paraventricular nuclear cells, × 900 from Fig F *O*—Mamillary nucleus, × 45, normal brain *P*—mammillary nucleus, × 45, Case I Note atrophy and loss of cells in the various nuclei from Case I exhibiting Cushing's syndrome when compared with the normal


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ticularly the paraventricular nuclei The supraoptic nuclei were only moderately depleted of cells.

Case V Female, age 32 months, weight, 29 pounds, well until 13 months before admission First a rapid gain in weight was noted, then hirsutism became apparent The clitoris enlarged and the voice became deep. Polydypsia, polyphagia, a plethoric appearance of the face, acne and cutis marmorata appeared

Physical appearance typical of Cushing's syndrome with virilism Blood pressure, 220/175, blood cholesterol, 225 mg per cent, serum chlorides, 657 mg per cent, blood potassium, 19 3 mg per cent, fasting blood sugar, 65 mg per cent, sugar tolerance normal, insulin tolerance slightly increased

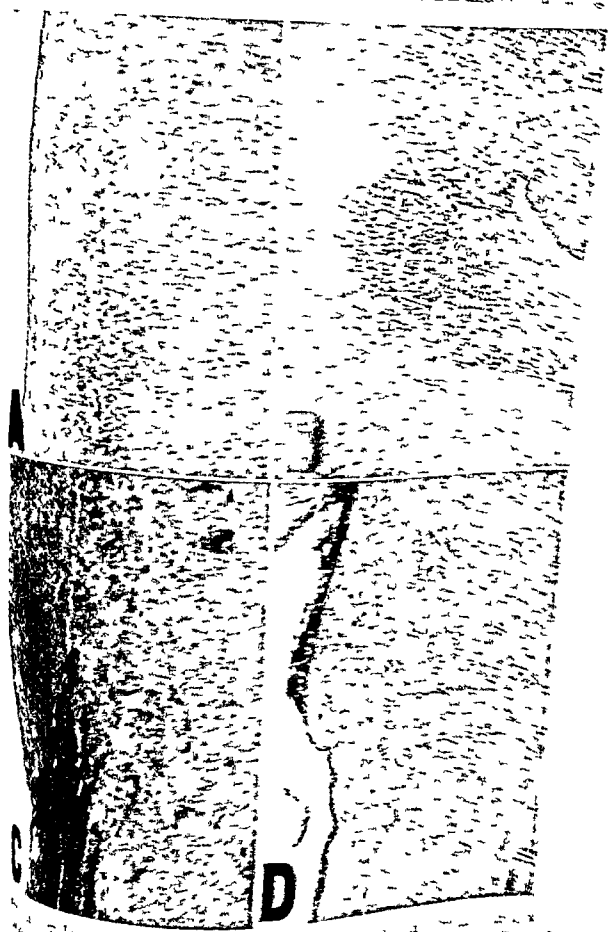
At operation a tumor of adrenal cortical origin was removed from the right side Examination showed it to be of the adrenal cortical type

Case VI Female, age 28 years, duration of illness, two years Signs and symptoms included the following full-moon face with hirsutism, acne and hemorrhagic skin lesions, mental depression, amenorrhea with loss of libido, polyuria, backache, apathy, obesity of the "buffalo" type, purple striae, blood pressure, 176/124, diabetes mellitus well developed only after two years of illness External and internal female organs normal X-ray studies showed osteoporosis of skeleton Essential autopsy findings malignant adrenal cortical tumor Hypophysis showed extensive hyalinization of basophil cells Serially cut sections of the hypothalamus revealed normal supraoptic and paraventricular nuclei (fig. 2)

On analysis of the pathological and clinical data, several facts appear of particular significance Hyalinization of the basophil cells is the one finding common to all autopsied cases The heretofore undemonstrated pathological changes, an atrophy of hypothalamus nuclei, particularly of the paired paraventricular nucleus, was present in four cases in which an adrenal tumor was not demonstrated. In the one adrenal tumor case in which the hypothalamus was studied it was found to be normal This finding lends support to the concept that while there may be several primary causes leading to Cushing's syndrome they probably all act to produce hyalinization of the basophil cells of the hypophysis via the adrenal cortex Clinically, the cases with an adrenal tumor showed signs and symptoms similar to those with a hypothalamic lesion except for an exaggeration of signs of virilism

In our series no case was available in which the typical symptom complex was associated with a tumor of the thymus The report of Crooke (1935, loc cit) that such a tumor in three persons with typical symptoms of Cushing's syndrome has been found associated with hyalinization of the basophil cells of the hypophysis, is accepted as evidence that certain thymus tumors are to be regarded as primary lesions in the pathogenesis of Cushing's syndrome Enlargement of the adrenals has been a constant finding in such cases Thompson and Eisenhart (6) also refer to a case of Cushing's syndrome in which at autopsy an arrhenoblastoma and hyalinization of the basophils were found The close chemical relationship between the hormones of the adrenal gland and those of the ovary would make such a finding not surprising

The cause of the atrophy of the hypothalamic nuclei, particularly of the paired paraventricular nucleus, is not known with certainty The atrophy of the ependymal lining cells of the third ventricle opposite the paraventricular nucleus found in all four of our cases suggests that some increased intraventricular pressure was present This is borne out by the autopsy records in which an internal hydrocephalus of mild degree was noted in three of the four cases In a recently observed case not included in our series, a typical clinical picture of Cushing's syndrome along with other neurological disturbances specifically referable to pressure on the upper spinal cord developed in a 33-year-old female during two years of illness. Examination revealed that this patient had a complete block of her spinal canal at the level of the second cervical vertebra, on lumbar puncture her spinal fluid pressure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cases that the atrophy of the hypothalamic nuclei is secondary to a chronic internal hydrocephalus of low degree Because nerve cells do not regenerate it follows also that in this case the depression of the paraventricular nuclear cells was in whole or in part functional

EXPERIMENTAL DATA

Basophil cell loss in hypophysis following hypothalamic injury

Changes in the hypophysis following a hypothalamic lesion involving the supraoptic and paraventricular nuclei will be reported on in two adult female dogs, K-20 and C-8, and one adult male dog #64 The lesion in each was made through the oral approach with a specially designed instrument The stalk was cut (a procedure which in itself does not lead to hyalinization of the basophils) and the hypothalamic tissue above and caudal to the stalk then curetted out Injury, if any, to the pars distalis was minimal Any dog so operated on will hereafter be referred to as a "puncture" dog The normality of the pars distalis was tested by renal function determinations which revealed normal diodrast and inulin clearances (White, Heinbecker and Rolf, 1943) (7) After operation the dogs had well developed diabetes insipidus and showed a considerable increase in body weight dog K-20, 59 per cent in 21 months, dog C-8, 52 per cent in nine months, dog #64, 24 per cent in seven months Dog K-20 was autopsied 21 months, dog C-8, nine months, dog #64 seven months after operation The results to be described are supported by autopsy material from many other dogs, some of the hypothalamic "puncture" type, some simply and others totally hypophysectomized Microscopic sections from the endocrine glands of ten male and of ten female normal dogs provided control material

The lesions in the hypothalamus were checked in serially cut 20 micron sections stained with cresyl violet (fig 2) In all three dogs there was marked destruction of the supraoptic and the paraventricular nuclei The hypophyses of dogs K-20 and C-8 were sectioned serially at five microns and the sections stained according to the method of Rasmussen The hypophysis of dog #64 was sectioned serially at 20 microns and similarly stained In both animals the eosinophil cells were normal in structure and relatively increased in number The chromophobe cells were not abnormal histologically There was a marked diminution in the number of the basophil cells (fig 3) The few cells of this type remaining showed a complete loss of granules with a homogeneous, turbid appearance of the cytoplasm The appearance of these cells differed from the hyalinized basophil cells of persons dying of basophilism in that such cells usually show the hyalin material in direct contact with some remaining normal granular cytoplasm The difference in the cytological picture of the basophil cells of the experimental animal and of persons with Cushing's syndrome may depend on a difference in degree of the hypothalamic injury or it may be a species difference A study of the cells in the experimental animal at different time intervals following the hypothalamic injury is in progress

The basis for the basophil cell loss in the puncture dogs has not been established with certainty A first suspicion naturally was that it was due to the stalk section By actual experiment it was established that stalk section in itself

does not cause basophil cell loss It was not possible experimentally to exclude the possibility that the total or nearly total loss of pituitary forming tissue might be responsible However, it is known that in women marked diabetes insipidus may exist without obesity and without interference with ovarian follicular function, as proven by their capacity to bear children Certain other inferences may be drawn from clinical and experimental data It is known that in cases

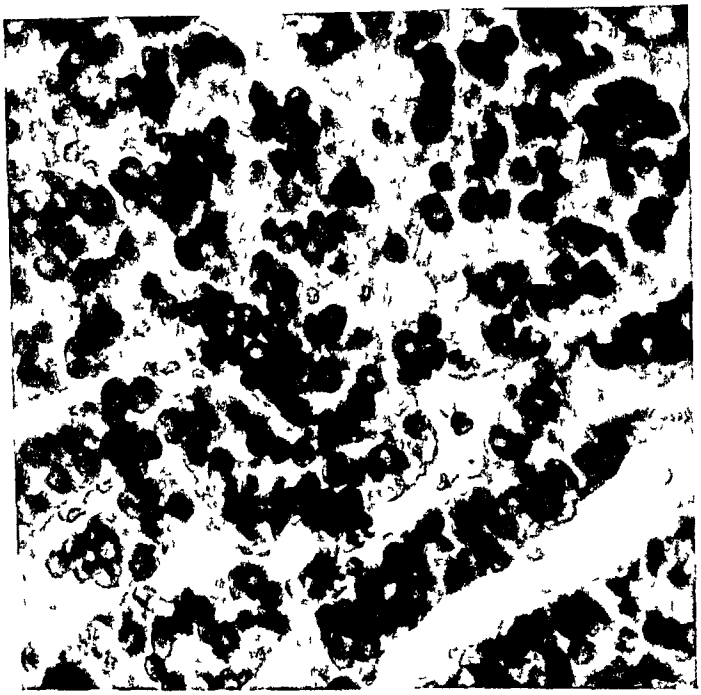

FIG 3 PHOTOMICROGRAPH × 680 FROM ANTERIOR LOBE OF HYPOPHYSIS OF K 20, SHOWING EOSINOPHILS AND CHROMOPHOBES WITH VERY FEW BASOPHILS REMAINING
Those present have lost their granules

of Cushing's syndrome due to an adrenal tumor hyalin degeneration of the basophil cells occurs with regressive changes in the thyroid and gonads similar to those which follow hypophysectomy in dogs Dogs with hypothalamic lesions resulting in degeneration of the paired paraventricular nucleus and with basophil cell loss are sensitized to exogenous cortical hormone as demonstrated by the degree of its influence on renal circulation and on certain renal tubular functions (Hombecker, Rolf and White, 1943) (8) Possibly therefore, in un-

balanced or exaggerated influence from the adrenal cortex is responsible for the basophil depression in puncture dogs

Changes in endocrine glands other than the hypophysis in dogs with hypothalamic lesions

Changes in the other endocrine glands of dogs K-20, C-8 and #64 are of particular interest in the problem of determining the pathogenesis of Cushing's syndrome Alterations are found in the thyroid, in the pancreas and in the gonads The adrenal glands are grossly and microscopically normal

The thyroid glands are grossly normal Microscopically the follicles containing colloid are seen mostly in the periphery of the gland and they are individually smaller than those of the usual normal (fig 4) The colloid in these is inspissated and then has a strong affinity for basic dyes The central region of the gland is filled with many small follicles, many without colloid, others with only a small amount There are many clusters of large acinar cells, some of them with a marked affinity for acidophilic dyes Often such cells were within the acini, but many appeared outside of them From a study of the sections the interpretation is made that the stimulus for normal secretory function is deficient In spite of the cellularity of the gland it does not have the appearance of an overactive gland such as seen in humans with exophthalmos and hyperthyroidism

Similar changes are found in the thyroid glands of simply and totally hypophysectomized dogs (fig 4) Supporting the impression that the glands so altered are not active is the level of the blood cholesterol which averages 200 mg per cent in all dogs with such hypothalamic lesions

Representative sections stained with hematoxylin and eosin, with Masson's stain and with the Mallory azan stain, from six regions of the pancreases of dogs K-20, C-8, #64 and of a fourth puncture dog still alive, K-18, in which the pancreatic tissue was obtained by biopsy (fig 5) show some hypertrophy and hyperplasia of the islets in two, (C-8 and K-18) and a marked atrophy and diminution in the number of the islets in the other two, (K-20 and #64) These conclusions are estimates arrived at from a comparison of the number and size of the islets in 20 normal stock dogs In the pancreases with well developed islets the individual cells, particularly the beta cells are normal in their cytological characteristics In the pancreases with small islets and a diminution in their number, many of the remaining cells, including the beta cells, show a lessening of the cytoplasm relative to the size of the nucleus The nuclei often are vesicular, the cytoplasm vacuolated In some cells inclusion bodies homogenous in appearance are visible The changes on the whole, however, indicate a quantitative reduction in the number of the islets and islet cells rather than a qualitative alteration

A similar apparent increase in the size and in the number of the islets is seen also in sections from the pancreases of simply and totally hypophysectomized dogs (fig 5) It seems probable, therefore, that any change in the pancreatic islets which follows the loss of the hypophysis is directly or indirectly due to the loss of the basophil cells because the puncture dogs showing changes similar

to the hypophysectomized dogs have a loss of basophil cells only It is quite possible that the changes in the islet cells recorded are an expression of a response to changes in other organs associated with carbohydrate metabolism While it may be that the first change is invariably a hyperplasia and hypertrophy to be followed later by an atrophy because of overwork or because of a general body degeneration it is not felt that our evidence is adequate to assert this

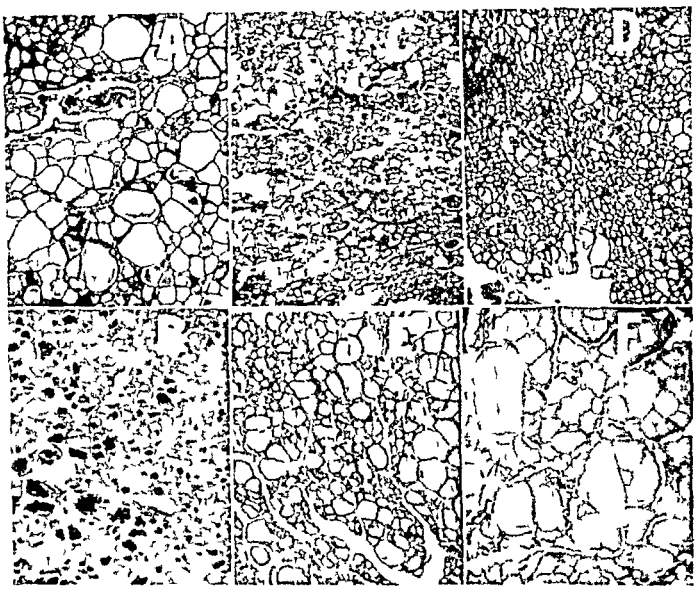

FIG 4 PHOTOMICROGRAPHS 50 DIAMETERS

1—normal dog thyroid *B*—thyroid dog 64 of the puncture type in which there was almost complete loss of basophil cells of hypophysis Note small acini poor colloid formation *C*—thyroid B-52 a simple hypophysectomy dog *D*—thyroid, K-17 a totally hypophysectomized dog 1 c, median eminence included Note similarity of structural changes in *B C* and *D* Inspissation of colloid with affinity for basic dyes is marked in *D* *E*—thyroid Case I note similarity to *B C* and *D* *F*—thyroid Case 4 showing low epithelium

The acinar cells are normal in all the hypothalamic puncture dogs They are normal also in the simply and totally hypophysectomized dogs In hypophysectomized dogs there is an increase in the amount of interacinar fibrous tissue, which may become marked in two years' time after the operation

Serial sections of the ovaries of K 20 (fig 6) and of C 8 reveal that follicular growth has not proceeded normally Few of the follicles have gone into the early vesicular state There is marked proliferation from the germinal epithelium into the tunica albuginea There were occasionally found several small ova within one atretic follicle There is an increase in the fibrous tissue and

smooth muscle layer Within the cortex there were large islets of yellow pigmented cells which are not associated with corpora lutea and which do not appear

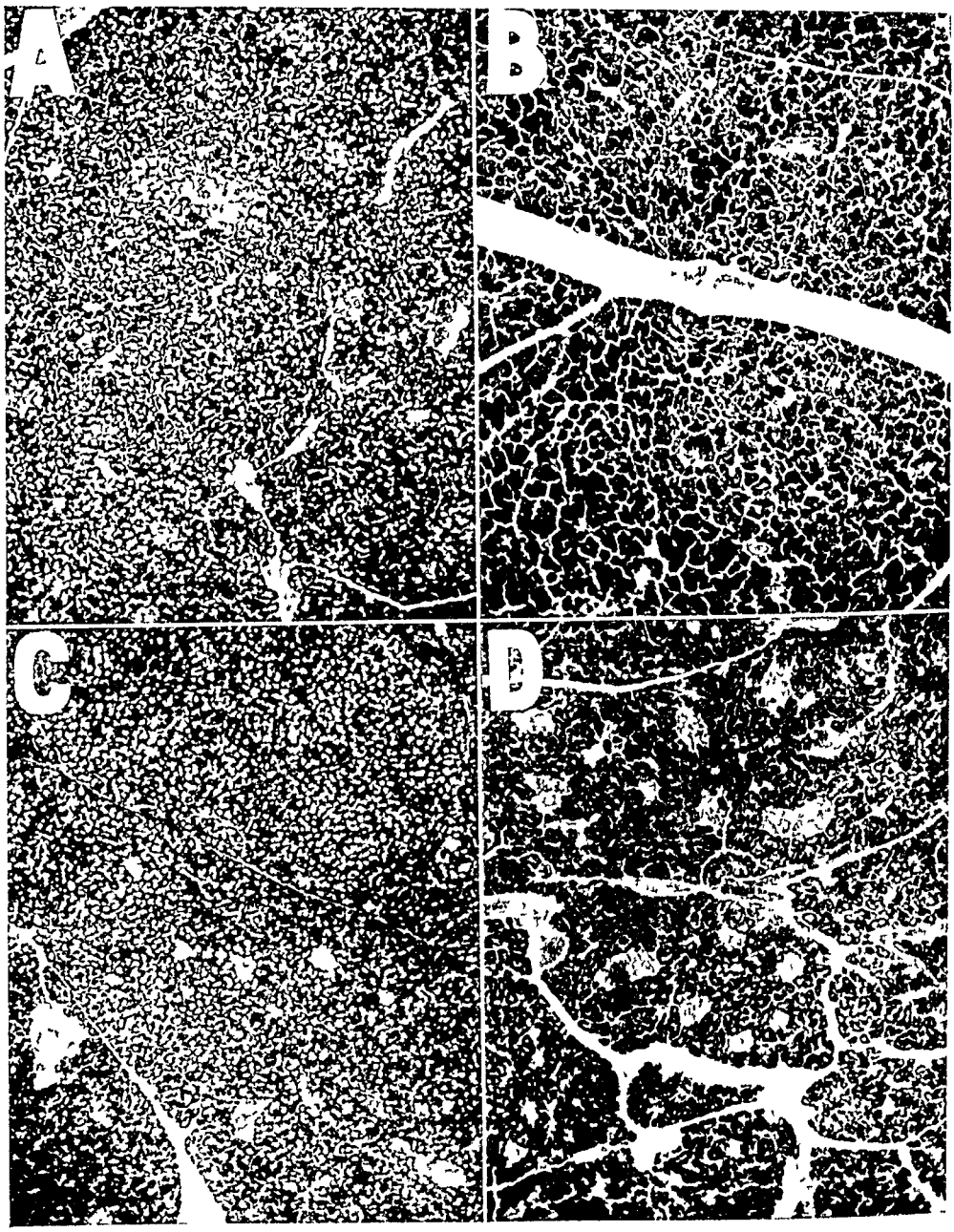

FIG 5 PHOTOMICROGRAPHS, 50 DIAMETERS

A—pancreas, normal dog *B*—pancreas, K-20, dog of the puncture type with almost complete loss of basophils of the hypophysis, islets small and few in number, dog obese but some beginning weight loss before sacrifice Acinar tissue normal *C*—pancreas, K-18, a markedly obese puncture dog still increasing in weight Islets somewhat hyperplastic *D*—pancreas from totally hypophysectomized dog, quite obese, no weight loss, islets hyperplastic and quite numerous

in normal ovaries so far studied They are regarded as interstitial cells It is concluded that in the ovaries follicular growth is initiated normally but that

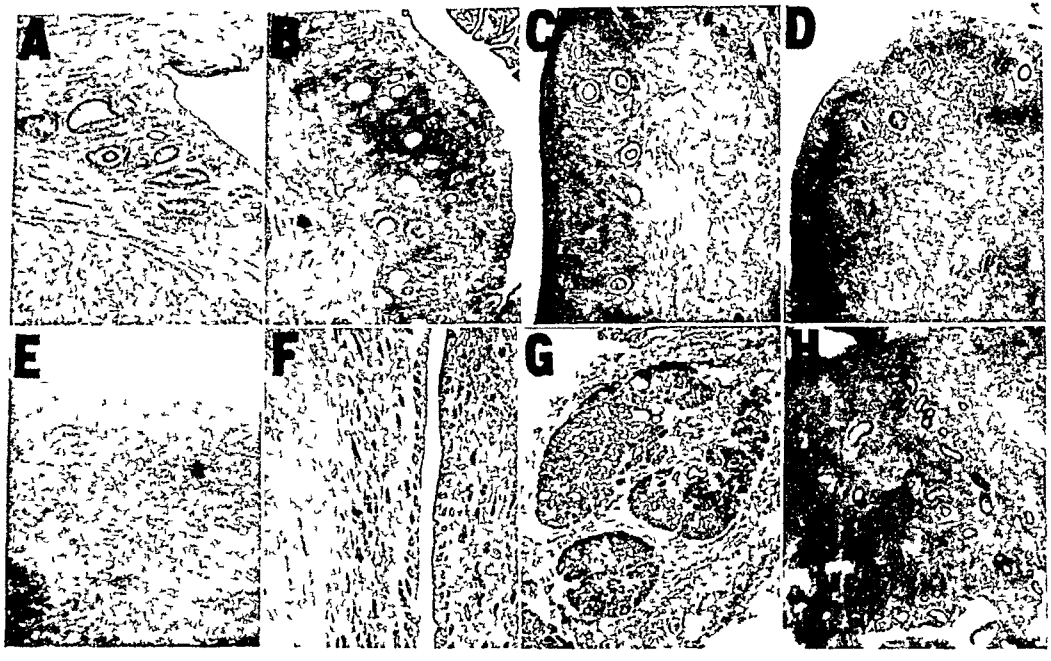

FIG 6 PHOTOMICROGRAPHS, 50 DIAMETERS

A—normal dog ovary B—ovary, dog K-20, puncture type C—ovary, dog K-21 from which the pars distalis and the posterior lobe were removed 21 months previously D—ovary dog K-15, totally hypophysectomized 9 months previously Note that in B, C and D there is a failure of follicular development, no mature graffian follicles are being formed In all, islands of pigmented cells are present These probably are of the interstitial type because as shown in I, the uterus is in a quiescent state and there is no activity in the breast tissue G, such as would be anticipated if they were corpora lutea or cells I—ovary, Case 2 H—ovary, Case 1 Note the absence of maturation of follicles in I and H, just as in B C and D

some stimulus to differentiation of the primordial follicles is lacking This stimulus normally comes presumably from the hypophysial basophil cells

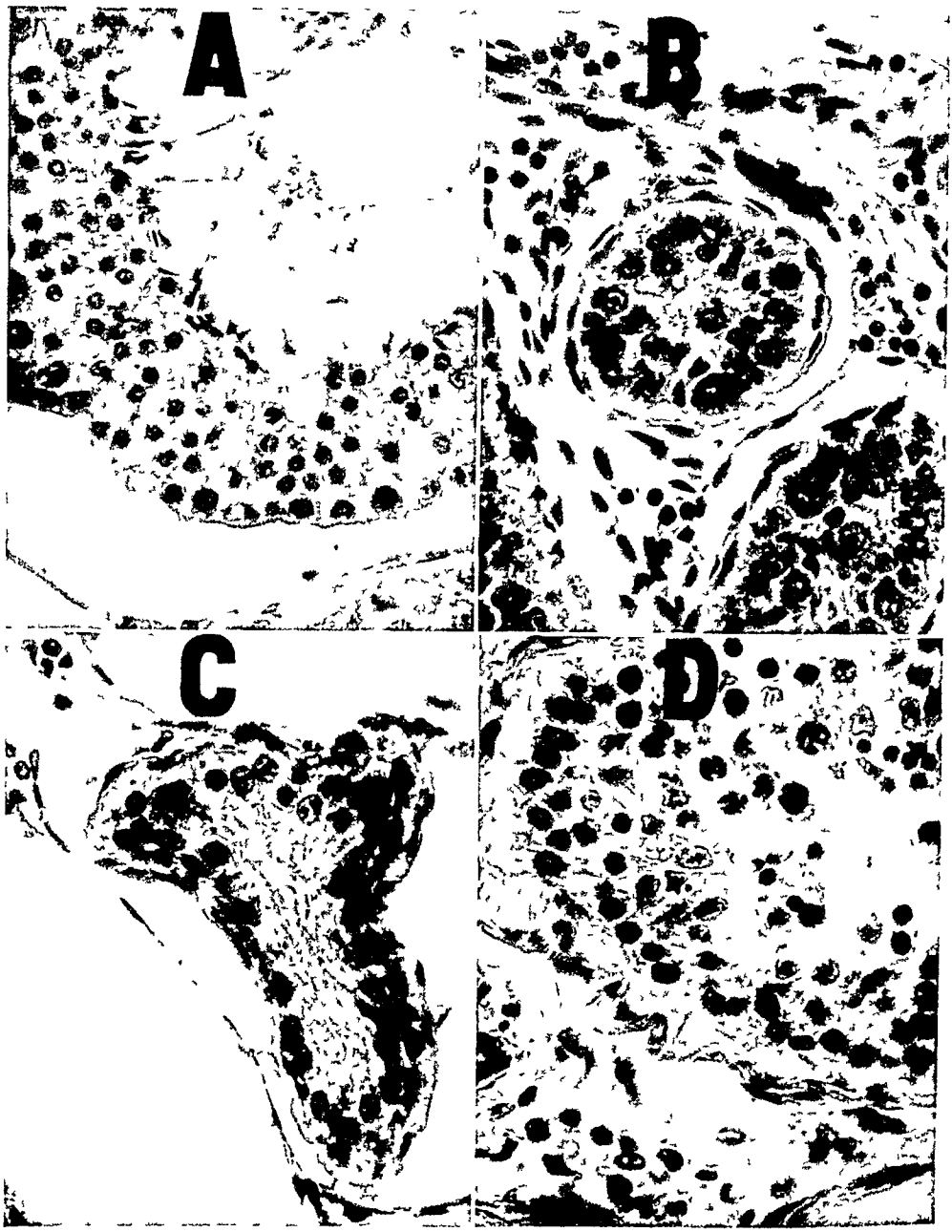

FIG 7 *A*—normal dog testis showing normal spermatogenesis *B*—testes, dog 64, showing primary and secondary spermatocytes but no spermatids Note interstitial cells are plentiful when compared with those in *C*, a testis of a completely hypophysectomized dog in which there also are no spermatids *D*—testis, Case 4, in which spermatogenesis is suppressed

Sections from the testes of dog #64 (fig 7) show a depression of spermatogenesis Primary spermatogonia are present but there is complete absence of

mitoses Secondary spermatogonia and spermatids are not found The Sertoli and interstitial cells are present at least in normal numbers

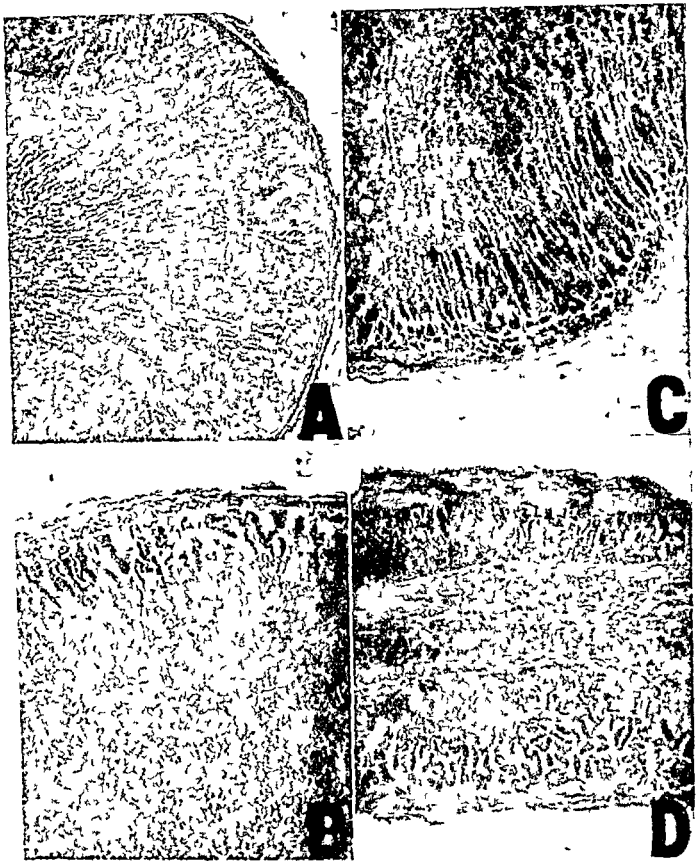

FIG 8 PHOTOMICROGRAPH 50 DIAMETERS

A—adrenal gland K 20, puncture type Note absence of cortical atrophy when compared with B B—adrenal normal dog C—adrenal Case I showing well developed cortical layers no adenoma D—adrenal totally hypophysectomized dog showing marked atrophy of all cortical layers

The adrenal glands in the three puncture dogs are grossly normal This was confirmed in the microscopic sections (fig 8)

CORRELATION OF CLINICAL AND EXPERIMENTAL DATA

Comparison of histological changes in endocrine glands of four cases of Cushings' syndrome showing hypothalamic lesions and those in dogs with similar experimentally produced hypothalamic lesions

The absence of normal follicular development and of normal spermatogenesis found in the ovaries and in the testes of the puncture dogs was found also in the human ovaries and testes of patients with Cushing's syndrome (figs 6 and 7)

The microscopic findings in the human thyroids (fig 4) are not entirely identical with those in the dog thyroids but in both the picture is interpreted as indicating a depression of activity In the human cases this is indicated by the low epithelium which lines the acini and by the density of the colloid contained therein, in the dogs by a failure of normal acinar formation and by a depression of colloid secretion

The histological changes in the human and the dog pancreases are in many respects quite similar In two of the four cases of Cushing's syndrome hypertrophy and hyperplasia of the islets were in evidence, in the other two the islets were considered normal but in one of these the pancreas weighed only 40 grams In two of the four dogs' pancreases hypertrophy and hyperplasia of the islets was diagnosed, in the other two the islets were small and few in number

Microscopically the adrenal glands of the experimental animals appear normal In the cases of Cushing's syndrome they were normal or hyperplastic (fig 8)

Obesity Obesity of the buffalo type in varying degrees is a constant finding in persons exhibiting Cushing's syndrome Investigations in this laboratory (Heinbecker and White, 1942, loc cit) to determine a basis for experimental obesity in the dog have yielded the following information obesity in the dog results after complete or partial destruction or retrograde degeneration of the paired paraventricular hypothalamic nucleus, particularly of its caudal portion Marked obesity results when destruction or denervation of the neuro hypophysis and a complete or partial destruction or retrograde degeneration of the caudal portion of the paraventricular nucleus coexist Removal of the *pars distalis in itself* results invariably in 20 to 30 per cent more increase in weight than occurs in spontaneously fat dogs after two years of caging The presence of the *pars distalis* in animals with complete or partial destruction or degeneration of the supraoptic and paraventricular nuclei is favorable to the development of marked obesity The results suggest that a lack or a marked lessening of the secretion of the neurohypophysis may aid in fat storage in the presence of a diminution in the number of cells of the caudal portion of the paraventricular nuclei

From other unpublished evidence obtained in this laboratory experimental obesity in the dog is held to be the result of a combination of factors among which are a depression of thyroid and gonadal activity and an increased effectiveness of the adrenal cortical hormone which follows after a hypothalamic lesion of the caudal portions of the paraventricular nuclei This may explain the greater obesity in dogs with such a lesion and in which the glandular hypophysis is not removed, for in such animals the adrenal cortex does not atrophy as it does in the totally hypophysectomized animal

On the basis of our animal experiments the hypothalamic lesions found in our four cases would explain the obesity in Cushing's syndrome

Obesity also is present in cases exhibiting Cushing's syndrome in which at autopsy an adrenal or thymus tumor is found Experimental and clinical evidence exists that the adrenal gland plays a significant role in fat and lipoid metabolism In experiments on the rat, Hewer (9) (1920) showed that the feeding of lipoid extract of the adrenal cortex of cattle may lead to marked obesity McKinley and Fisher (10) (1926) noted an increase in weight of 10 per cent in rats fed adrenal cortex for eleven weeks Also, it is known that in hyperinterrenalism leading to precocious puberty in children there is associated obesity, the fat deposits accumulating in the back and trunk and with special pads over the breasts The bull neck and the full-moon face are conspicuous and the red cheeks are indicative of the children's plethora In the later stages of the disease, the obesity may yield to emaciation

Direct information is to the condition of the hypothalamic nuclei in cases exhibiting the obesity of Cushing's syndrome where a tumor of the thymus was found is not available However, there is no reason to suspect a hypothalamic lesion in view of its absence in cases associated with an adrenal cortical tumor The mechanism of the development of obesity is probably similar in all cases of Cushing's syndrome, i e, a combination of factors particularly those arising from changes in thyroid, gonadal and adrenal cortical activity

Water balance Disturbances in the water balance is evidenced by polydipsia and polyuria are very frequently exhibited by persons with Cushing's syndrome Such symptoms are explainable on the basis of the pathological findings and experimental evidence In dogs diabetes insipidus follows the denervation or destruction of the pituressin forming tissue (Hembecker and White, 1941) (11) The pituressin forming tissue, i e, the neural division of the hypophysis is innervated by fibers from cells in the supraoptic and rostral division of the paraventricular nuclei For total diabetes insipidus, i e, a urine output of 15 to 20 times the normal, the entire neurohypophysis must be completely denervated If 15 per cent of the tissue remains with its nerve supply intact, diabetes insipidus does not result

In our four cases of Cushing's syndrome in which hypothalamic lesions were encountered, the degree of cell loss in the supraoptic nuclei harmonized with the degree of polydipsia and polyuria found clinically

In the two cases in which an adrenal tumor was the primary cause of the syndrome, periodic polyuria of moderate degree was encountered As stated, in the one case of this type in which the hypothalamic nuclei were examined, there was no evidence of cell loss in the supraoptic or paraventricular nuclei, consequently, the action of the hormone from the adrenal tumor must either be a direct one on the kidney tubules or indirect in whole or part through a neutralization of pituressin

Hypertension The experimental work of Goldblatt and his associates (1934) (12) has lent support to the concept that essential hypertension in man follows spastic or occlusive disease of the renal arteries While in hypertensives the arterial disease is generalized, it is the renal involvement which probably is

essential for the activation of those mechanisms involved in elevating the blood pressure and in increasing the work of the heart necessary to maintain a normal blood flow

In three of the four cases in this series in which the kidneys were available for study, there was marked occlusive disease of the renal vessels In the fourth case (#1) only slight thickening with a minimal degree of medial necrosis was recognizable in the larger renal vessels by ordinary histological methods Micro-incineration of these vessels (fig 9) showed a definite increase in calcium and magnesium salts in the wall of the vessels Such a change is known to characterize arteriosclerotic vessels and in the aorta has been shown to be associated with a diminution in extensibility This, together with the slight narrowing of the lumen due to a thickening of the walls, would lead to a diminution in pulse pressure within the kidney with each heart systole and thereby to an increased output of renal vasopressor substance (Kohlstaedt and Page (13), 1940) It is held then, that the degree of renal damage in all our four cases is adequate to explain the development of hypertension found clinically

'Puncture' dogs have not developed hypertension in two years of observation Their mean blood pressure averages 140 mm Hg, which is higher than the average for hypophysectomized dogs, 105 mm Hg Such dogs do not in that time period develop arteriosclerosis

Demineralization of skeleton In a high percentage of the cases exhibiting Cushing's syndrome extensive demineralization of the skeleton is found whether due to an adrenal or thymus tumor or to a lesion of the hypothalamic nuclei After two years of observation this has not been noted in dogs with comparable hypothalamic lesions In case IV of our series in which the clinical observations extended over many years there appeared to be a correlation between the time of development of the demineralization of the skeleton and of the arteriosclerosis In our dogs, as before noted, well developed arteriosclerosis does not occur It is suspected that the existence of arteriosclerosis may be a *sine qua non* for skeleton demineralization

Diabetes mellitus Diabetes mellitus is regarded as a disorder of metabolism secondary to a deficient supply of insulin or to changes in other organs which depress its effect While in some instances the primary seat of the deficiency is undoubtedly the pancreas, it is recognized that disturbances in the liver and in other endocrine glands may make manifest or augment the insulin deficiency Obesity, arteriosclerosis and fatty infiltration of the liver are characteristically found in persons with diabetes mellitus and with Cushing's syndrome While diabetes mellitus is present in many cases of Cushing's syndrome, in two of our series there is recorded an increased tolerance for sugar, in one of these diabetes mellitus later developed, concurrently with the development of obvious arteriosclerosis

Examination of the pancreases in two of the cases of this series in which diabetes mellitus was present affords no ready anatomical basis for assuming an insulin deficiency True, in case I, the pancreas weighed only 45 grams but the islets in the remaining tissue were described as normal In case IV there was focal hyperplasia of the islets In neither of the cases did the islets show

hydropic degeneration nor was there conspicuous loss of granules in the beta cells It seems more probable that the insulin secreted was inadequate for the maintenance of normal carbohydrate metabolism due to obesity or to fatty

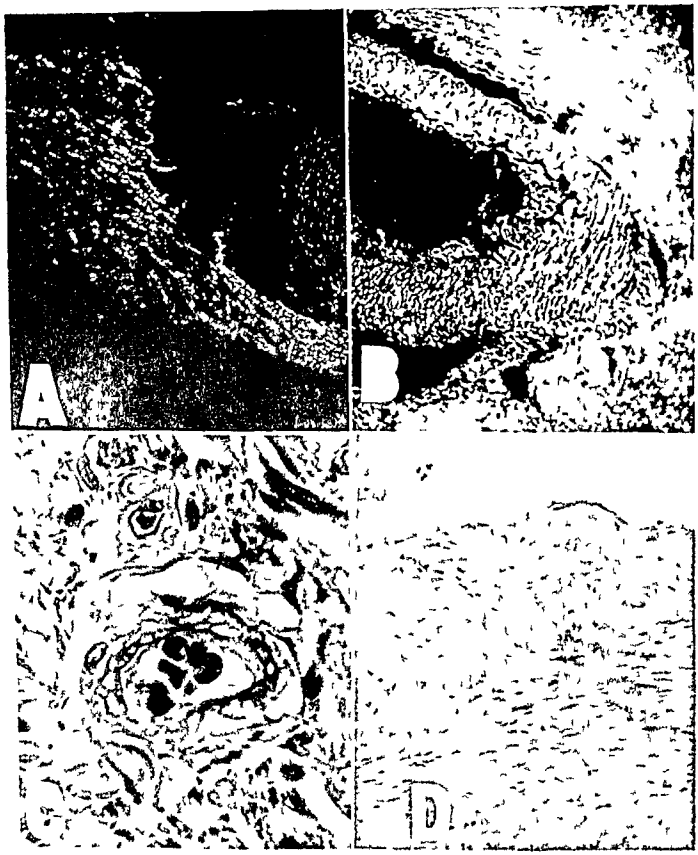

FIG 9 PHOTOMICROGRAPHS × 250

A microincrustated interlobular renal blood vessel wall from normal person 38 years of age B—microincrustated interlobular renal blood vessel from Case I of our series Note microcrystals chiefly calcium and magnesium in B C—photomicrograph × 930 of blood vessel wall from skin of Case I Note large cells which special stains have shown to be filled with neutral fat and cholesterol D—photomicrograph × 50 of a portion of femoral artery from Case I showing well marked arteriosclerosis

infiltration into the liver cells, to arteriosclerosis or to some other tissue or endocrine disturbance

In none of the puncture dogs, even when the islets became atrophic has

betes mellitus developed These dogs show a normal or decreased insulin sensitivity and a normal or increased sugar tolerance The liver glycogen content after fasting is normal or above the average normal and they do not succumb to hypoglycemia with several days of fasting They differ from human beings among other things in that they do not develop definite arteriosclerosis This may be significant in that diabetes mellitus in man so frequently manifests itself after, or possibly coincidentally with, the development of arteriosclerosis

Blood vessel changes Cutis marmorata, so frequently noted in cases of Cushing's syndrome, indicates a hyperdynamic response of the blood vessels of the skin to cold In other diseases where skin vessels exhibit such hyper-responsiveness to cold, there is an associated hyper-responsiveness to nervous and humoral vasoconstrictor influences (Heinbecker and Bishop (14) 1935) While it is recognized that the abnormal response of skin vessels does not necessarily indicate a similar abnormality in the visceral vessels there is no *a priori* reason against it The probability of its occurrence in Cushing's syndrome is indicated by the fact that the deposit of neutral fat and cholesterol noted in the skin blood vessels also exists in the visceral blood vessels Of interest in this regard is the experimental evidence of Schmidtmann (1925) (15) that rabbits fed large amounts of cholesterol to produce arteriosclerosis exhibit an exaggerated elevation of blood pressure on the administration of exogenous epinephrine The blood vessels of such animals exhibit the same infiltration with fat and cholesterol as do the blood vessels of persons exhibiting Cushing's syndrome Apparently, the pathological process which ultimately leads to arteriosclerosis and to hypertension may serve as a basis for the hyperdynamic responsiveness of the blood vessels to vasoconstrictor influences

Generalized arteriosclerosis has been found in all of our cases of Cushing's syndrome Sections of the skin, particularly from areas not involved in acute inflammatory processes, when stained with osmic acid and Sudan III to identify neutral fats, and treated with the Schultz modification of the Liebermann-Burchard test for cholesterol, show an infiltration of neutral fat and cholesterol into the cells of the blood vessels The neutral fat and cholesterol are found in the endothelial lining cells of the smaller blood vessels and in large xanthoma-like cells which appear in the inner and outer layer of the vessels Degenerative and hyperplastic changes proceed simultaneously to produce ultimately the picture of arteriosclerosis The change regarded as primary is the infiltration of neutral fat and cholesterol into the endothelial and xanthoma-like cells Presumably, it is brought about by the change in metabolism associated with Cushing's syndrome Particularly significant is the depression of thyroid function exhibited by such patients Kountz and Hempelmann (1940) (16) reported that three of four patients with essential hypertension totally thyroidectomized in the hope that their hypertension would be relieved, died within a year of rupture of the aorta because of medial necrosis

Changes in the skin Microscopic studies of the skin from case I and V revealed marked fatty infiltration and a marked deposit of cholesterol in the outer third of the dermis The fat was demonstrated by staining with osmic acid and Sudan III, the cholesterol by the Liebermann-Burchard method The latter

method appears to be sufficiently specific to warrant the statement that the lipoid deposited in the tissues of our cases is chiefly cholesterol There is a marked destruction of the collagen fibers in the dermis This permits stretching of the skin with thinning when fat is deposited in large amounts in the subcutaneous tissues The blood vessels of the skin show intimal cell hypertrophy with marked infiltration of fat and the presence of much cholesterol in these cells (fig 9) The intimal thickening leads to a narrowing of the lumen of the vessels In the areas of the skin in which the vascular lesions are well developed degenerative changes in the collagen fibers also appear The collagen fibers are infiltrated with fat and cholesterol and ultimately may become completely broken up The extent to which these changes depend upon changes in blood supply is not certain Deposits of fat and cholesterol also are seen early in the neurilemmal sheath cells Both in the endothelial lining of the blood vessels and in the nerve sheaths atypical foam cells are seen They are not as numerous, however, as in typical xanthomatous lesions of the skin

Similar infiltration with lipoid occurs in the skin, the blood vessels and the nerve sheaths of dogs rendered obese by appropriate hypophysial and hypothalamic lesions

DISCUSSION

The evidence indicates that a loss of basophil cells in the hypophysis leads to regressive changes in the thyroid and the gonads while leaving intact the adrenal cortex Changes also may occur in the islets of the pancreas These may show hypertrophy and hyperplasia or atrophy with a diminution in their number Such findings all lend strong support to the hypothesis of Crooke that hyalinization of the basophil cells is a most significant lesion in the pathogenesis of Cushing's syndrome because on the basis of our experimental evidence it should lead to those changes in the endocrine glands which especially are found at autopsy in persons exhibiting the syndrome The changes are such as to afford a basis for a satisfactory explanation of most of the complex of signs and symptoms which characterize the state The basophil cell change is believed effected through an unbalanced influence from the adrenal cortex This imbalance can be of two kinds, one is excess secretion from the adrenals, the other, normal secretion acting on an hypophysis sensitized to adrenal cortical hormone The first or excess secretion may be due to hyperplasia or tumor formation in the adrenal gland, the second is illustrated in the case of Cushing's syndrome with paraventricular nuclear atrophy and normal adrenal glands, or in the dog with paraventricular nuclear destruction or denervation and normal adrenal glands Differences in symptomatology, particularly those referable to the sex function and masculinization, probably are due to differences in the effectiveness of or in the amount of available androgens, brought about by the many alterations in endocrine function and balance associated with the syndrome

The original concept of Cushing that the syndrome follows from an overactivity of the hypophysis, particularly overactivity of the cells in a basophil adenoma, is no longer tenable It is common to have basophil adenoma of the hypophysis without Cushing's syndrome or hyalin degeneration of the basophil

cells. Recent studies of the function of the hypophysis also are in conflict with such an interpretation They indicate rather that we are dealing with a condition of underactivity of the gland The lowered basal metabolic rate, the high blood cholesterol and the depression of sex function are regularly seen in the experimental animal after removal of the hypophysis It is rather to be suspected that the somewhat high statistical incidence of basophil adenoma found in cases of Cushing's syndrome is indicative of an attempt to compensate for the depression of basophil cell function

SUMMARY

Clinical and experimental studies pertaining to the pathogenesis of Cushing's syndrome are reported

At least three primary lesions, a tumor of the adrenal cortex, a tumor of the thymus, or an atrophy of the nuclei of the hypothalamus, particularly the paraventricular nuclei, are the probable precursors of the hyalinization of the basophil cells of the hypophysis, such as have been described by Crooke and Rasmussen

It is suggested that the hypothalamic atrophy may be secondary to a low degree of internal hydrocephalus Such depression is at first functional and later structurally detectable

In the one adrenal tumor case available for study, the hypothalamus appeared normal

Dogs with an experimental lesion of the hypothalamus involving areas similar to those found involved in four cases exhibiting Cushing's syndrome, show a marked loss of basophil cells with degenerative changes in the remaining basophil cells in the hypophysis

In such animals changes occur in the thyroid, in the gonads and in the islets of the pancreas of a type which serves to explain many of the symptoms of Cushing's syndrome

Experimental evidence is offered to show that at least two of the primary lesions referred to above could be expected to cause a disturbance of lipid metabolism characterized by an accumulation of fat and cholesterol in the adipose tissue of certain regions of the body In dogs with complete or partial bilateral destruction of the caudal portions of the paraventricular nuclei there is just such an infiltration of fat and cholesterol into tissues such as the skin, the muscles, the liver and the walls of the blood vessels as occurs in persons exhibiting Cushing's syndrome

The disturbance in fat metabolism resulting in the accumulation of lipoid and fat in the cells of the blood vessel walls leads to the development of arteriosclerosis

Disturbances in water balance result from either of two causes, (1) the direct or indirect effect of the secretion from the adrenal cortical cells or adrenal cortical tumor cells, or (2) from a decrease in secretion of the neurohypophysis resulting from degeneration in the supraoptical hypophysial system

The factors concerned in the pathogenesis of the hypertension and of the diabetes mellitus in these cases are discussed

ACKNOWLEDGMENT

I am indebted to Dr Cyril M MacBryde for the use of the clinical records of the first three cases of our series and to Dr Charles H Eyermann for the use of the record of Case 4 Dr Robert A. Moore permitted me the use of the general autopsy findings of the first four cases and I am grateful to him for his permission to section and study the brains from these persons Dr A T Rasmussen, Professor of Anatomy, University of Minnesota, kindly sent me sections from the hypothalamus and the record of Case 6 Without his material this presentation would have been greatly hampered

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THE AEROBIC NON-HEMOLYTIC STREPTOCOCCI

A Critical Review of Their Characteristics and Pathogenicity with Special Reference to the Human Mouth and to Subacute Bacterial Endocarditis

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Aerobic streptococci which either fail to change blood or induce greenish discoloration of blood—the gamma and alpha varieties, respectively, as defined by Brown (1)—are indigenous parasites of mucous membranes They are commonly looked upon as the most characteristic members of the normal flora of the mouth and throat Lewkowicz (2) found them to be predominant in the oral flora of nurselings, and Brailovsky-Lounkevitch (3) and others have reported that they are the organisms most constantly recovered from the mouth both in early and in adult life Buchbinder, Solowey and Solotorovsky (4) were able to recover greening streptococci from the air, particularly of enclosed places of human congregation, and believed that their concentration in air was an index of the degree of contamination derived from the human nasopharynx Torrey and Lake (5) have proposed an air pollution test based on this view, and Dick and Hucker (6) have suggested that a presumptive test for oral contamination of drinking utensils might be based on the recovery of salivary streptococci from them

Although they are normal parasites, the non-hemolytic streptococci have also been implicated as disease agents in such common oral disorders as dental caries and periapical abscesses, and in many extra-oral diseases, including those that have been ascribed to focal infection from the mouth or other mucous membranes It is one of the purposes of this review to reconsider the evidence for such pathogenicity, not specifically for each disease entity, but in general with reference to the disease-producing capacity of the organisms The somewhat specialized question of their role in dental caries will be discussed elsewhere, (7) while the major disease entity with which these organisms are clearly associated, subacute bacterial endocarditis, will be reviewed in detail As a basis for consideration of their role in disease, the classification, characteristics and interrelationships of the non-hemolytic streptococci are discussed with major emphasis on the streptococci of the mouth

CLASSIFICATION

The primary criterion for the classification of streptococci as a whole is that of hemolytic capacity, as defined originally by Schottmuller (8) and amplified by Smith and Brown (9) and by Brown (1) With certain exceptions those forms that induce true (beta) hemolysis include the more active pathogens of man and animals, while those that fail to induce this change comprise the saprophytes

and normal parasites with which this review is concerned The finer classification of the former group is accomplished effectively in modern practice by application of the serological methods of Lancefield (10) and Griffith (11), but subdivision of the non-hemolytic group, lacking comparable means, remains at present in an unsatisfactory state The extensive and painstaking studies of Sherman and his collaborators (12, 13) are of great value toward this end The nomenclature proposed by these workers is followed here, although it is admittedly not without defects It may be noted, for example, that the specific term *Streptococcus viridans* (8) originally used to designate a greening form, has been abandoned, but that a "viridans" group is defined, although essentially without reference to greening on blood as a differential character *Streptococcus salivarius*, the commonest single variety in the viridans group, has been characterized in a recent paper by Sherman, Niven and Smiley (13) as being nearly uniformly anhemolytic or gamma Such usage seems ambiguous, even though these workers have presented cogent evidence to justify it, as noted below

Sherman (12) recognizes four general divisions among the streptococci as a whole· 1) the *pyogenic* group, which includes most of the hemolytic and all the actively pathogenic streptococci, 2) the *viridans* group, comprising the characteristic parasites of the human mouth and throat and other forms, 3) the *lactic* group, consisting of saprophytes found especially in milk, and 4) the *enterococcus* group, made up of streptococci chiefly of fecal origin The major criteria for this subdivision are ability to grow (a) at 10°C and 45°C and (b) in the presence of 6 5 per cent NaCl, or 0 1 per cent methylene blue, or at pH 9 6, (c) strong reduction, and (d) ammonia production The pyogenic group is generally negative in all these tests except production of NH_3, members of the viridans group may grow at 45°C but not at 10°C and are negative in all other tests, the enterococcus group is usually positive in all tests, while the lactic group grows at 10°C but not at 45°C and is found to have other properties intermediate between those of the viridans and the enterococcus groups All three groups other than the pyogenic group include both alpha and gamma streptococci, the enterococcus group, in addition, includes certain beta-hemolytic varieties

THE VIRIDANS STREPTOCOCCI

The organisms included under this head are essentially parasites on the mucous membranes of the mouth and upper respiratory passages of man and animals, less commonly of the intestinal and genito-urinary tracts In the former locations they can be found normally in nearly all instances Wright (14) has pointed out that their growth on solid media resembles that of the pneumococcus, being less vigorous than either the fecal or the hemolytic streptococci, but the viridans forms do not show the autolytic depression characteristic of aging pneumococcus colonies They prefer enriched media and are often difficult to maintain in subculture

Streptococcus salivarius is the commonest viridans variety found in the human mouth and throat Safford, Sherman and Hodge (15) studied 322 strains of *St salivarius* from healthy throats and classified them into five groups. Group

I comprised 290 of the strains and was homogeneous They grew in milk as short chains of rather large cocci On blood agar they produced greening often weakly, some strains were anhemolytic A few strains grew at temperatures as high as 45°C, but none grew at 10° or at 47°C and none survived heating for 30 minutes at 60°C They produced final pH levels ranging from 4 4 to 4 0, did not produce ammonia or liquefy gelatin, and fermented dextrose, maltose, lactose and sucrose but not glycerol, starch or mannite Litmus milk was acidified and coagulated and later reduced, sodium hippurate was not hydrolyzed These group I strains grew poorly and tended to die out, they were more delicate than hemolytic streptococci and distinctly more so than other non-hemolytic varieties The 32 strains not included in group I were heterogeneous, some produced a high final pH (4 9 to 5 2) and were more actively green-producing (group II), others were weakly hemolytic (group III), others produced ammonia (group IV), and one strain failed to ferment lactose or to acidify milk (group V)

Niven, Smiley and Sherman (16) have reported another differential characteristic of *Str salivarius* which may have value for rapid identification When grown on well buffered agar containing 5 per cent of either sucrose or raffinose, they appear as mucoid colonies as large as colonies of colon bacilli or yeasts, apparently because of the production of considerable amounts of a polysaccharide Under these conditions such large colonies were not produced by hemolytic streptococci of any of the Lancefield groups, nor by enterococci or lactic streptococci, nor by other varieties of the viridans group except *Str bovis*, which occasionally formed similar colonies The production of a polysaccharide and of large mucoid colonies had previously been reported for unidentified streptococci by Oerskov (17) and Oerskov and Poulsen (18) Niven, Smiley and Sherman (19) found the polysaccharide of *Str salivarius* to be a soluble levan, whereas that produced by *Str bovis* is an insoluble dextran

In a later paper, Sherman, Niven and Smiley (13) reemphasized the homogeneity of *Str salivarius* They found that among 331 non hemolytic streptococci from human throats, 184 could be selected as *Str salivarius* on the basis of polysaccharide production from sucrose These 184 strains all grew at 45°C but not at 10°C in both broth and milk, they all gave final pH values in dextrose broth between 4 4 and 4 0, all fermented inulin, raffinose, sucrose, maltose and salicin, split esculin, but failed to ferment mannite, sorbitol, glycerol, arabinose or xylose Sixteen of these strains failed to ferment lactose, and 14 were negative in trehalose All but 5 per cent of the strains were indifferent (gamma) with respect to blood, and none were strongly alpha Smiley, Niven and Sherman (20) noted that *Str salivarius*, thus defined, could be grown on a synthetic medium containing inorganic salts, glucose, sodium thioglycolate and 7 amino acids (glutamic acid, leucine, isoleucine, arginine, lysine, methionine and tyrosine), with the addition of riboflavin, nicotinic acid, pantothenic acid, thiamin, biotin, and uracil Among other streptococci tested, only two strains of *Str bovis* were able to grow on this medium, and one of these could grow without riboflavin It is noted that these growth requirements further distinguish *Str salivarius*

from mitis strains, which failed to grow in the synthetic medium, and also from enterococci, as noted below

The propriety of designating as *Str salivarius* an organism that nearly always fails to induce greening of blood requires confirmation This organism appears to be a distinct and homogeneous entity, but its relationship to forms previously designated by the same name remains to be determined

Streptococcus mitis is redesignated by Sherman, Niven and Smiley (13) as the heterogeneous viridans streptococcus of mouth and throat, following the name given by Andrewes and Horder (21) for a group originally poorly defined The species is defined by the later workers on negative grounds it fails to form polysaccharide from sucrose and does not ferment inulin Its other characteristics, aside from those that conform with the viridans group as a whole, are variable Of the 147 strains studied, about 90 per cent were strongly alpha, few were completely gamma Most strains yielded higher terminal pH values than *Str salivarius* and failed to curdle milk It may be noted that all of the 331 throat strains obtained by these workers could be placed in either the salivarius or the mitis categories

Streptococcus bovis appears to be the predominant form in the mouths and intestines of cattle It is also found in the human intestine Sherman (12) reported that 10 strains of the streptococcus isolated by Bargen (22, 23) from cases of ulcerative colitis in man agreed generally with his criteria for this species *Str bovis* is closely related to *Str salivarius*, but the former has a higher maximum temperature of growth, a distinctly higher thermal resistance, and usually hydrolyzes starch As noted above *Str bovis* may produce mucoid colonies on buffered 5 per cent sucrose agar, but these are associated with a polysaccharide distinct from that produced by *Str salivarius*

Streptococcus thermophilus This distinctive streptococcus grows actively at 50°C , although not at 53°C , does not grow below 20°C , and is the most heat resistant of the streptococci, surviving temperatures as high as 65°C It has been isolated only from milk and milk products Sherman (12) includes it among the viridans streptococci because of its inability to grow at low temperatures or under other conditions mentioned above which permit the growth of lactic streptococci and enterococci

Streptococcus equinus is distinguished from the other members of the group by its inability to ferment lactose, and by other characteristics, such as ability to grow in bile It is the predominating streptococcus in the intestine of the horse, and has also been isolated from bovine and from human feces Lactose negative non-hemolytic streptococci isolated from the human mouth and throat, however, were found to correspond in other characteristics with *Str salivarius* or *Str mitis* (Sherman, Niven and Smiley (13))

THE LACTIC STREPTOCOCCI

The milk streptococci, other than *Str thermophilus*, are distinguished as a group by their ability to grow at 10°C but not at 45°C They are generally intermediate in resistance between the viridans and the enterococcus groups,

but seem more closely related to the latter They are usually inactive on blood, but may produce greening These are the common milk souring organisms The two species in the group, *Streptococcus lactis* and *Streptococcus cremoris*, are apparently true saprophytes, found only on plants and in milk They may be distinguished by the inability of *Str cremoris* to form ammonia from peptone, and by finer criteria given by Sherman (12)

Niven (23a) has reported that *Str lactis* requires at least 14 amino acids for prompt growth All of 21 strains required pantothenic acid, nicotinic acid and biotin, and some strains failed to grow without thiamin and riboflavin *Str cremoris* seemed to have similar growth requirements

THE ENTEROCOCCI

These typically short chained oval streptococci are particularly characteristic of the lower intestine of man and other warm-blooded animals, but they may also be found on other mucous membranes Porch (24), for example, found that of 100 strains of streptococci isolated from the genito-urinary tract, 73 were anhemolytic *Str fecalis*, 3 were *Str liquefaciens*, 5 were alpha *Str fecalis*, and the remaining 19 were alpha streptococci of the viridans group Dible (25) noted that the enterococci are more easily maintained in culture than other streptococci, are more active fermenters, and are generally more resistant As a group they are the most resistant of the streptococci Although they are typically anhemolytic or gamma, many strains may show greening, sometimes only on heated blood agar Two beta hemolytic species—*Str zymogenes* and *Str durans* —are included in this group because of agreement in their other characteristics It is noted below that these organisms as well as members of the viridans group may be the causative agents of subacute bacterial endocarditis

Most strains of both the hemolytic and non hemolytic varieties of enterococci have been found to contain the group D carbohydrate of Lancefield (26, 27, 28, 29, 24)

Woolley and Hutchings (30) were able to grow *Str zymogenes* luxuriantly in a synthetic medium containing inorganic salts, glucose, and 6 amino acids (isoleucine, lycine, tyrosine, arginine, tryptophane and glutamic acid), with the addition of riboflavin, pantothenic acid and pyridoxin Sulfur was also required, either as inorganic sulphide, or as cystine or methionine, and ferrous iron was listed as essential This medium also supported the growth of group B hemolytic streptococci, but was not satisfactory for other pyogenic species Schuman and Farrell (31) extended these findings to *Str fecalis*, which was found to require tryptophane and the same vitamin B fractions Valine, however, was used successfully in place of isoleucine and lycine The nutritive requirements of the enterococci thus differ from those of *Str salivarius*, which requires a different group of accessory substances (nicotinic acid, thiamin, biotin and uracil, not pyridoxin) and does not require tryptophane [1]

[1] Niven and Sherman (31a) have recently reported different findings with 19 strains of enterococci including members of all 4 species All 19 required biotin nicotinic acid, calcium pantothenate and pyridoxin 17 required riboflavin and 7 required folic acid, none

Streptococcus fecalis The typical non-hemolytic enterococcus which fails to liquefy gelatin has been studied most completely by Sherman, Mauer and Stark (32), who reported an analysis of 434 strains The species is on the whole very homogeneous *Str fecalis* occurs usually in pairs, less often in short chains, and resembles the pneumococcus morphologically but does not appear encapsulated It grows at both 10°C and 45°C, and is generally resistant to high pH levels, high concentrations of sodium chloride, and other conditions which prevent growth of streptococci of other groups Final pH values in dextrose broth were found to range from 4 4 to 4 0, like those of *Str salivarius* Glucose, maltose, lactose and salicin were fermented, but fermentation reactions were otherwise not characteristic Some strains hydrolyzed sodium hippurate This organism grows readily on simple media, although it may prefer reduced oxygen tension on primary isolation

The resemblance of *Str fecalis* to *Str lactis* in morphology, heat resistance and other respects, which gave rise in the past to the view that they were identical (33, 34, 35), is now dismissed by Sherman (12) on the seemingly cogent ground, among others, that the lactic streptococcus is a true saprophyte, whose rare occurrence under parasitic conditions seems attributable merely to survival, whereas the enterococcus is a true parasite of the intestinal tract The Lancefield D carbohydrate, moreover, has not been found in *Str lactis* (29)

Streptococcus liquefaciens differs from *Str fecalis* only in that the former liquefies gelatin, being virtually identical in all other respects, including the finer criteria given by Sherman It is an intestinal parasite

Streptococcus zymogenes is the typical beta-hemolytic enterococcus of the human intestine Sherman includes both gelatin liquefying and nonliquefying strains within the species Its hemolytic activity does not seem to confer on it any pathogenic power distinct from that of other enterococci

Streptococcus durans is a beta-hemolytic species, extracts of which react weakly with group D sera (12), which differs from *Str zymogenes* in its lesser reducing activity, uniform inability to liquefy gelatin, and narrower range of fermentations It occurs in the human intestine and is also widely distributed in milk and milk products It is not pathogenic for laboratory animals and has not been associated with human disease.

SEROLOGY

The separation of beta hemolytic streptococci and pneumococci into distinct categories (groups, types) by serological means has been of immense practical significance Attempts to apply similar methods to the non-hemolytic streptococci, however, have not yielded comparable results Early workers found the mouth streptococci to be serologically heterogeneous by several immunological methods, including agglutination (36, 37), agglutinin absorption (38, 39),

required thiamin Moreover, the amino acid combinations used by the previous workers were found insufficient for any of these strains, 17 grew in a medium containing 13 amino acids, and for one strain of *Str zymogenes* valine, leucine, isoleucine, glutamic acid, arginine and tryptophane were found essential

complement fixation (40, 41), and precipitation (42) Grumbach and Schnetz (43) found that 156 strains of enterococci were heterogeneous by agglutination and cited earlier literature to similar effect Kinsella and Swift (40) and Hitchcock (44) demonstrated group reactions among hemolytic and non-hemolytic streptococci and among streptococci and pneumococci, and Lancefield (45) showed these cross reactions to be due to protein antigens At the same time Lancefield noted the presence in *Str viridans* of highly specific antigens of probable carbohydrate nature Hitchcock (46) was able to place about 50 per cent of nonhemolytic, inulin fermenting streptococci (presumably *Str salivarius*) into a single type by means of precipitin and agglutination reactions, the remaining strains being heterogeneous Endo (47) reported that streptococci isolated from saliva and from common pathological processes of the mouth could be classified by agglutination absorption into four groups Kiuchi (48) in a study of 76 strains isolated from 12 persons, extended the number of groups to 13 and later (49), with 157 strains from 9 persons, to 23

The most complete serological classification of the greening streptococci thus far reported is that of Solowey (50), who studied over 200 strains Of these 108 had been isolated from the blood in subacute bacterial endocarditis, 99 were obtained from human throats and extracted teeth, and 15 were derived from the vaginas of young infants and children All strains appear to have been alpha streptococci More than three quarters of them, other than those of vaginal origin, were *Str salivarius* as determined by Sherman's earlier criteria, but whether the others belonged in Sherman's viridans group is uncertain [2] Only two strains out of the total number reacted with Lancefield group serums, these fell into groups G and K, respectively Of the remainder, 66 per cent could be classified into 14 serological groups, two of which (groups I and II) comprised about 50 per cent of the reacting strains from each source The 15 vaginal strains were tested against only four of the group sera, one of these reacted weakly with group I serum, while the others failed to react with any It is noteworthy that no consistent serological difference could be found between the strains isolated from pathological or from normal sources, and that no correlation was demonstrable between the biochemical and the serological groupings The fact that none of Solowey's strains reacted with Lancefield group D sera may have depended upon her selection of alpha colonies, other workers, as noted below, have frequently found enterococci in endocarditis blood The possession of this specific carbohydrate, at all events, seems to mark the enterococci off as a distinct immunological group Sherman, Niven and Smiley (13) have reported that 83 of 184 strains classified as *Str salivarius* on the basis of polysaccharide production from sucrose fell into a single type by precipitation, but details were not given, and up to the present time these findings have not been correlated with those of Solowey Whether Sherman's other specific distinctions can be validated by serological means thus remains to be determined For the present these distinctions are acceptable as matters of convenience, but the viridans

[2] As noted above, the criteria for *Str salivarius* were more sharply defined by Sherman, Niven and Smiley (13) after Solowey's data were published

group appears to be a broad and complex category, and its final classification has evidently not yet been achieved

METABOLISM

Relation to Oxygen The streptococci (other than the anaerobic forms, with which this review is not concerned) seem to grow equally well under aerobic and anaerobic conditions, although some varieties (e g *Str fecalis*), may be favored by anaerobic conditions on primary isolation Their metabolism is essentially of the anaerobic type, with lactic acid the predominant product of sugar breakdown In general they show little oxygen uptake (51), are relatively insensitive to hydrogen peroxide (52) and do not contain iron-porphyrin enzymes such as cytochromes or catalase (52, 53) although cyanide-sensitive systems of unknown nature may be present (54) They require riboflavin for growth, contain flavoprotein enzymes (55) and generally produce hydrogen peroxide (52) Certain species or strains are exceptional in one or more of these properties, for example, strains of hemolytic streptococci of group A, type 3 do not form peroxide (56, 57) Otherwise these characteristics are compatible with Dixon's (58) Type 4 respiratory chain, in which flavoproteins are figured as mediating between the substrate-coenzyme-protein system on the one hand and molecular oxygen on the other, and in which, in the presence of oxygen, hydrogen peroxide is formed (see also Baumann and Stare (59)) This would be a type of metabolic habit intermediate between that of such true aerobic bacteria as *Escherichia coli*, which contain iron-porphyrin enzyme systems, and that of the true anaerobes, which are incapable of aerobic growth for reasons that remain obscure Close relatives of the streptococci with regard to these properties are the pneumococci and the lactobacilli (7) It may be noted that the so-called lactic acid bacteria, used in the commercial production of lactic acid, include members of both the streptococcus and the lactobacillus groups

Lactic Acid Production Friedemann (60) found that *Str viridans*, growing in buffered broth with 0 9 per cent dextrose, formed chiefly lactic acid, with small amounts of formic and acetic acids and ethyl alcohol, these products together accounting for 80 to 95 per cent of the sugar carbon Smith and Sherman (61) have reported a detailed study of lactic acid production in 0 1 per cent dextrose broth by a wide range of streptococci The results obtained were similar under aerobic and anaerobic conditions The average yields of lactic acid ranged from 81 8 per cent for group F pyogenic streptococci to 96 6 per cent for *Str lactis* The hemolytic group in general gave lower yields than the other groups, and the viridans, lactic and enterococcus groups differed only slightly among themselves These findings are in general accord with the final pH values in dextrose broth given by the different kinds of streptococci

The nature of the green pigment produced by streptococci from blood is obscure It was formerly believed to be methemoglobin, a brownish oxidation product of hemoglobin. Anderson and Hart (62), however, showed that pneumococci formed an olive green precipitate when grown in broth with laked blood, and formed the same pigment when either crystalline hemoglobin or methemoglobin

was substituted for the blood The pigment was thought to be an iron containing derivative of hemoglobin, but was evidently not methemoglobin A green pigment spectroscopically similar to that produced in pneumococcus cultures could also be obtained with *Str viridans*, *Str fecalis* and with hemolytic streptococci, as well as with such unrelated bacteria as *Staphylococcus aureus* and *Escherichia coli* A similar pigment was also formed, moreover, without bacteria, by addition of a reducing system such as ascorbic acid or cysteine glucose, aerobically in the presence of alkaline potassium phosphate It was concluded that greening depends on an oxidation reduction brought about by a bacterial dehydrogenase The absence of greening in blood agar cultures of hemolytic streptococci was attributed to dilution or destruction of hemoglobin in the neighborhood of colonies resulting from hemolysis

There is much evidence, on the other hand, that greening is associated with production of hydrogen peroxide by the bacterial cells Brown (1) had assumed that viridans streptococci form two substances in sequence, a hemolysin (hemotoxin) and a substance responsible for greening, the latter being elaborated first and interfering with the action of the hemotoxin, which, acting preferentially at low temperatures, was thought to be responsible for the peripheral hemolysis that may appear after refrigeration McLeod, Gordon and Pyrah (63) and others had found that peroxide forming bacteria yielded greening in heated blood agar, in which the catalase contained in the red cells had been inactivated Hagan (64) believed that the greening effect produced by typical viridans streptococci was due to peroxide and acid, the former yielding discoloration but protecting the cells against acid hemolysis Peripheral hemolysis after refrigeration was considered to be due to diffusing acid, acting only after peroxide production had diminished or ceased A similar view has been advanced more recently by Fuller and Maxted (65), who reported that hemolytic streptococci produced hemotoxin one to three hours before peroxide appeared, whereas greening variants of hemolytic streptococci, which yielded only one quarter to one sixth as much hemotoxin, formed both substances at the same time Peroxide was found to inhibit hemotoxin formation, apparently by inducing retardation of growth Fuller and Maxted found that viridans streptococci produced so much peroxide that, when grown in mixed culture with a hemolytic strain, no hemotoxin could be demonstrated According to these workers greening is produced only by peroxide formers, and only with good aeration, thus accounting for the reappearance of hemolysis with alpha variants of hemolytic streptococci when grown in poured blood agar cultures They suggest that peroxide is destroyed only when catalase is first liberated from the red cells by action of the hemotoxin They found that added catalase prevents greening, and argued that "in cultures of green variants the appearance of peroxide before hemolysis has taken place results in the formation of green or brown pigments upon which the very weak hemolysin cannot act"

There is reason to believe that greening is not a uniform phenomenon Pneumococci, for example, sometimes produce a deeper-hued green than do viridans streptococci, and Mellon and Cooper (66) have described the production of a

"grass-green" zone by a variant of a hemolytic streptococcus Davis and Rogers (67) have recorded the production in blood agar cultures by saprophytic lactic acid bacteria of an uncolored zone of "bleaching" in which the cells are decolorized with little or no evidence of hemolysis Possibly such variations may have influenced the different results given above In any event, the question of the nature and origin of the green pigment must for the present be considered unsettled

INTERRELATIONSHIPS AMONG THE STREPTOCOCCI

Specific distinctions among the streptococci, like biological distinctions generally, are matters of convenience, and usually imply landmarks along a continuous range of variation rather than well separated categories. The occurrence of intermediate forms, and evidence of variation suggesting the possible transformation of species, continue to harass the taxonomist, and it is becoming increasingly clear that such phenomena are in the nature of things and cannot be ignored. The similarity of *Str lactis* and *Str fecalis*, for example, has already been considered Sherman discounts it on apparently valid grounds, but the possibility seems of interest that one form is or has been derived from the other by adaptation to a saprophytic existence in milk, or to a parasitic existence in the intestinal tract

Several workers have suggested a somewhat similar relationship between the greening and the hemolytic streptococci Rosenow (68) claimed to be able to induce the transformation of alpha to beta streptococci at will Other workers (69, 1) considered such a change extremely rare Greening variants of beta-streptococci, however, are well recognized Valentine and Krumweide (70) found such variants in 1 out of 21 strains of beta streptococci. These variants bred true and continued to resemble the beta variants in fermentation reactions and serologically, but they were reduced in virulence for mice Grinnell (71) reported that 2 of 4 beta streptococci from scarlet fever showed alpha colonies which bred true Of six pure line strains of alpha streptococci developed by single cell isolations from these strains, only one was virulent for mice with a very large inoculum (2 cc), whereas the beta strains were uniformly virulent in doses of 0 1 cc No reversion was noted The alpha variants were believed to resemble *Str. viridans* in all respects Citovicz (72) stated that alpha variants could be produced from scarlet fever strains of hemolytic streptococci by incubation for 24 hours at 37°C with scarlatinal antiserum, followed by chilling without freezing at −17°C. in capillary tubes The greening forms appeared on subculture to blood media Fuller and Maxted (65) confirmed the occurrence of the beta-alpha transformation, noted that group specificity was retained, and found that beta hemolytic activity returned upon cultivation in deep agar or under anaerobic conditions Working with such greening variants, Fuller and Maxted (65) as noted previously, obtained data which suggested that the transformation can be interpreted merely as a diminution of hemotoxic capacity, which when normally developed masks the greening mechanism The requirement of full aeration for greening is thus advanced to explain the reappearance of hemolysis under

reduced oxygen tension Lancefield (73) notes that non-hemolytic strains with apparently identical serological characters have been common in group B Completely non-hemolytic members of group A are rare, but Todd (71) has observed the transformation of hemolytic group A strains into greening variants by passage through mice, and Fry (75) has described alpha variants which were of the same serological type as hemolytic strains isolated from the same patient Like the greening variants studied by Fuller and Maxted, Fry's strains were hemolytic when grown anaerobically

It is of course uncertain whether these findings are applicable to greening streptococci as a whole, or only to greening variants of hemolytic streptococci They suggest a possible mechanism however, whereby one group might become transformed into the other

Another possible interrelationship in this group is that between the greening streptococci and the pneumococci This transformation was also claimed by Rosenow (68) among others and is likewise doubted by Wright (14) It is known that rough pneumococci may become bile insoluble or bile resistant Gorander (76) reported the transformation of streptococci isolated from subacute bacterial endocarditis into encapsulated cocci, soluble in bile salts, and with greatly increased mouse pathogenicity These strains did not agglutinate with pneumococcal type antiserums On prolonged cultivation, such a "transformed" organism became avirulent and bile insoluble, but cross agglutinated with a similarly retrograde type II pneumococcus Paul, Dedrick and Krumweide (77) also produced rough variants of pneumococci which were bile insoluble and seemed indistinguishable from certain strains of *Str viridans*

The foregoing data are suggestive but need not be taken too seriously as a basis of broad implications The fecalis lactis transformation has not actually been observed The beta-alpha change seems to occur, although not often, and the alpha variants may not be true *Str viridans* It is possible that greening streptococci and pneumococci may revert to a common form under exceptional circumstances

The possible interrelationship between non-hemolytic streptococci and lactobacilli is discussed elsewhere (7)

PATHOGENICITY

Evidence is presented below which leaves no doubt that both the viridans and the enterococcus groups of streptococci are capable of producing disease in man *under suitable conditions* Suitable conditions are clearly essential It is plain that mere inoculation of such streptococci, by any route and in any number, is rarely if ever sufficient to establish infection Some of the conditions that make infection with these bacteria possible have been attributed to the streptococci themselves, but on doubtful grounds, for the most part they are known to be dependent upon the physical state of the host

Pure cultures of both viridans streptococci and enterococci are usually entirely non-pathogenic for laboratory animals (78, 14) Mice are generally unaffected by subcutaneous or intraperitoneal inoculation even of large doses, with occa-

sional exceptions whose significance is uncertain. This lack of pathogenicity may be compared with the marked sensitivity of the mouse to the related hemolytic streptococcus, and its extraordinary sensitivity to the pneumococcus Guinea pigs are also refractory to greening streptococci

Subcutaneous inoculation of rabbits is usually without effect, but intravenous injection of large doses in these animals, and also in dogs, as noted below, may be followed by non-suppurative lesions of the joints, by fatal endocarditis, or occasionally by other lesions Generally such a result requires either repeated inoculation or preliminary traumatization, or other unusual procedures Moon and Stewart (79), for example, were able to produce a nonpurulent arthritis in all of four 10-week old pups, and in 3 of 4 rabbits, by inoculation of viridans streptococci freshly isolated from the blood of a patient with subacute endocarditis The inoculation was made both intravenously and by simultaneous implantation of an infected cotton plug in the peritoneal cavity Streptococci were recovered from the joint fluid, but not from the blood, peritoneal fluid, urine or other locations Cultures maintained for five weeks on artificial media were said to become avirulent Cecil, Angevine, and Rothbard (80) have reported similar findings Gross et al (81) produced vegetative endocarditis and a more or less lasting bacteremia in 28 per cent of rats by repeated intracardiac injection of viridans streptococci These workers reported that the animals responded with a transient leucocytic and predominantly monocytic reaction, such as would characterize the response of an immune or partially immune host to a pathogen of relatively low virulence

Rosenow, who in 1910 (82) confirmed the report of Horder (83) that greening streptococci can produce endocarditis in rabbits, has been identified with the view that the pathogenicity of these organisms depends upon characteristics of the parasite rather than of the host Rosenow's concept, which has been developed in several of his papers (84, 85, 86) has two aspects of interest in this connection (a) that the greening streptococci rapidly lose virulence on artificial cultivation, and (b) that their virulence is manifested not only by the development of lesions, but by a tendency, more or less characteristic of the strain, to localize in certain particular tissues or organs after intravenous inoculation The first consideration led this worker to use primary cultures, which were apparently often mixed and inadequately identified as to content, for animal inoculations The second, the principle of "elective localization", gave rise to a long series of reports by Rosenow and others which indicated that cultures derived from the "focus" (e g teeth or tonsils) in patients with such diseases as chronic arthritis, gastric or duodenal ulcer, or appendicitis, had a greater tendency when inoculated intravenously into rabbits to localize respectively in the joints, the stomach or duodenum, or the appendix, than elsewhere The use of mixed cultures obviously makes it impossible to determine the part played in these phenomena by any one constituent of the mixture For example, Rosenow (87) states that:

"all the cultures of streptococci manifesting a preference for anaerobic conditions in the primary culture ultimately became aerobic when, with few exceptions, they resembled Streptococcus viridans"

It is thus not always certain that the organisms described as "streptococci" or "diplococci" actually belonged to the group here under consideration The concept of elective localization has not been widely accepted Some of the diseases included by Rosenow as of streptococcal origin, such as poliomyelitis (88), herpes zoster (85), and encephalitis (89), are now known to be due to viruses, and none of the others has as yet been shown unequivocally to be caused by streptococci

Evidence obtained in more recent years strongly suggests that the pathogenicity of these streptococci depends not on aggressive factors of virulence in the parasite but on changes in the host which may be grouped under the general head of lowered resistance Schottmuller (90) and Lehmann (91) found that non-hemolytic streptococci are destroyed or grow very slowly in human defibrinated blood, whereas hemolytic streptococci grow in it readily Stiles and Chapman (92) have nevertheless suggested that ability of greening streptococci to resist the bactericidal action of fresh whole guinea pig blood may be used as an *in vitro* test of "probably pathogenicity" Friedman, Katz and Howell (93) found that viridans streptococci grow in normal serum, and are not inhibited by the presence of specific antibodies, since they grow in serum from immunized dogs and in that from human subjects with endocarditis (which contains specific antibodies) They are not inhibited by red cells and grow luxuriantly in fibrin, but they are inhibited by white cells and do not grow in whole blood in agitation These findings point to a fundamental difference in virulence factors between the greening and the hemolytic streptococci Strains of the latter group which are pathogenic for man elaborate substances such as hemotoxin, erythrogenic toxin, leucocidin, and hyaluronidase or spreading factor, and the bacterial cells contain a protein antigen (M substance) which is present in virulent but absent from avirulent organisms Such substances have not been associated with the greening streptococci,[3] and if these bacteria are subject to the fluctuations in virulence or in tissue localizing capacity as Rosenow suggests, the basis of such variation remains entirely unknown On the other hand, data given below show that the pathogenicity of the greening streptococci for both experimental animals and man has been definitely associated with changes in the resistance of the host It seems significant in this connection that the streptococci which have been incriminated in subacute bacterial endocarditis evidently do not belong to any one especially pathogenic variety but include members of both viridans and enterococcus groups This disease, moreover—the only one for which fully convincing evidence implicates the non-hemolytic streptococci—has been produced in experimental animals with pure cultures which, according to Rosenow, would have been completely lacking in virulence

Finally, by a curious paradox, the role of non hemolytic streptococci in subacute bacterial endocarditis, as detailed below, is not such as to suggest that these bacteria are active pathogens, or that they are necessarily involved in other disease processes The part played by the causative agent seems to be a passive

[3] The characteristics of the alpha change in blood suggest the presence of a weak hemotoxin, but no direct evidence for the existence of this or other viridans (or enterococcus) toxins is known

one, dependent upon pre-existing cardiac defects in the host, while the organism seems called upon only to be able to proliferate in fibrin, which also protects it against phagocytosis by the white cells of the blood In the secondary embolic phenomena to which the severity and fatality of this disease appear to be due, moreover, a similar mechanism seems to operate, and there is no evidence that the causative streptococci themselves have any capacity for invasion or destruction of host tissues

These considerations are not intended to close the door on the possibility that non-hemolytic streptococci participate in human infections other than subacute bacterial endocarditis, but they suggest that the burden of proof for such pathogenicity must rest with those who insist upon it It may be noted that Hadley and Wetzel (94) have reported that a rough variant of an alpha streptococcus isolated from the blood of a patient with a "rapidly developing" subacute bacterial endocarditis could be increased in mouse virulence by repeated passage. The freshly isolated smooth culture killed mice in 17 to 40 hours after intraperitoneal inoculation of 0 0025 to 0 005 cc The rough variant had an m l d of about 0 7 cc at first, but after passage became smooth and eventually (after 38 passages) attained an m l d of 0 0000001 cc Unfortunately the original strain was not identified beyond the statement that it produced faint greening at first and subsequently showed atypical hemolysis, and that in morphology it resembled the enterococcus The initial virulence of the smooth form suggests that the organism was not a typical member of either viridans or enterococcus groups If this observation can be duplicated with true non-hemolytic streptococci it will reopen the problem of the virulence of these organisms to study by a fresh approach

Dental Infections A long list of workers have reported the isolation of greening streptococci, sometimes of anhemolytic streptococci, from all the common infections of the mouth, including dental caries, pulpitis, periapical infections, and gingival and periodontal infections References to this literature are given by Appleton (95) Whether these bacteria play any role in the production of such lesions nevertheless remains obscure Although many reports indicate that greening streptococci were recovered from such sources in pure culture, this finding may reflect only the exclusive use of an aerobic cultural method like the streaked blood agar plate Many other microorganisms, which fail to grow under such conditions, are probably invariably present in all these lesions The pathogenic capacity of some of these other microorganisms is by no means insignificant Appleton's view (95) that only the streptococci among this complex flora are "pyogenic" is not supported by the evidence which clearly links the non-hemolytic streptococci only with non-suppurative processes, nor by other evidence that the so-called fusospirochetal flora, for example, (which apparently need not include aerobic streptococci) is capable of producing suppuration (96) The available data are inadequate to decide this question, but their tendency may be said to suggest that the greening streptococci are not more than secondary invaders in complex mixed infections if indeed they contribute to such infections at all

The mere association of greening streptococci, then, with periodontal, periapical, or other dental and oral lesions cannot be accepted as adequate evidence of a causative relationship Convincing evidence of causation requires experimental reproduction of such lesions in animals, by the use of pure cultures under suitable conditions of control, in accordance with Koch's postulates Failure to induce such experimental disease is of course not conclusive, but success would provide the only fully satisfactory means of resolving the question

Peculiar difficulties attend the accomplishment of this objective in relation to diseases of the mouth The mucous membranes are invariably contaminated to begin with, generally with the very bacteria under test, and no satisfactory way of obtaining durably sterile fields for such tests is known, short of the use of bacteriologically sterile animals (Reyniers (97)) There are in consequence no relevant data relating to gingival and periodontal lesions As for infections of the normally sterile pulp and periapical tissues, additional difficulties arise The tooth pulp, because it is completely encased by unyielding calcified dentin, and perhaps for other reasons, has extremely limited capacity for repair and reconstitution after injury, even in the absence of infection An injured pulp, indeed, even though sealed with aseptic precautions, is likely to become infected spontaneously, and in such infection viridans streptococci and other indigenous microorganisms of the mouth are likely to be present Without adequate uninfected controls, therefore, even the production of pulpitis or periapical abscesses with pure cultures of streptococci, and the subsequent recovery of the organism from the lesion, is inadequate evidence of a causative relationship An example of a carefully controlled experiment will make this point clear Genvert, Miller and Burn (98) removed pulps aseptically from the teeth of monkeys, sealed the cavities, and six days later reopened them and introduced a suspension of *Str viridans* The cavities were then closed with amalgam, in some instances with a "thin plate of non-bactericidal metal alloy inserted between the amalgam and the pulp chamber" Abscesses developed in several instances after a minimum of 17 days, and *Str viridans* was recovered from some of these, but others, similarly treated, yielded hemolytic streptococci and colon bacilli In a series of control teeth prepared in the same way but inoculated only with sterile salt solution, a few abscesses also developed, and *Str viridans* was also recovered from these These results suggest an anachoretic effect (99, 100, 101, 102) an injured or inflamed area tends to attract and fix microorganisms and other materials, presumably from the circulating blood It is clear that the findings permit no conclusion with regard to the ability of non-hemolytic streptococci to induce dental lesions

Influence of Bacterial Allergy A mechanism alternative to that which operates in subacute bacterial endocarditis, and which suggests an additional role of greening streptococci in human disease, is that of sensitization Like other foreign antigenic material, bacterial substance is capable of eliciting an antibody response, which may be demonstrated in animals under suitable conditions by allergic manifestations Greening streptococci are not exceptions to this rule It is important to note that such allergic phenomena have no necessary relation-

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Andrewes, Derick and Swift (104) reported that the intradermal injection of greening streptococci into rabbits was followed in some instances after about a week, without other treatment, and after the slight inflammatory response to the injection had subsided, by the appearance of a spontaneous "secondary reaction" at the site of the injection The reaction was obtained by the use of both living and heat-killed greening streptococci, and also with certain other members of the streptococcus group and with pneumococci, but not with typical human hemolytic streptococci, *Neisseria catarrhalis*, or *Escherichia coli* The development of the reaction coincided with the appearance of general hypersensitivity, demonstrable by ophthalmic reactions following corneal inoculation, by increased reactivity of the skin, and occasionally by lethal reactions following intravenous inoculation (105) McLeod and Finney (106) were able to produce nephritis in rabbits by following the line of these studies They sensitized 33 rabbits by repeated intradermal inoculation of living viridans streptococci at weekly intervals, and then injected large doses of the homologous organism directly into the renal artery The use of living cultures for these renal injections often resulted in death, heat-killed suspensions were therefore used in most instances, and it is noted that the results obtained with completely killed suspensions were similar to those that followed the use of suspensions in which some organisms had survived the heat treatment Acute exudative and proliferative glomerulitis was produced in the kidney on the injection side in 15 of 33 sensitized rabbits and in 4 of 20 unsensitized animals No relation could be demonstrated between the occurrence of renal lesions and the presence of general hypersensitivity as shown by skin or eye tests The possible role in these phenomena of greening streptococci indigenous to the animal does not seem to have been considered

An allergic reaction analogous to the Koch phenomenon in tuberculosis, characterized by an inflammatory response which limits the spread of infection following inoculation in a sensitized animal, has been reported for both virulent and avirulent hemolytic streptococci by Angevine (107, 108) An opposite effect due to non-bacterial sensitization has been described by Weisberger (109, 110), who found that simultaneous intravenous injection of horse serum and viridans streptococci resulted in longer persistence of streptococci in the blood in rabbits previously sensitized to horse serum than in normal rabbits Weisberger also observed that organisms could be disseminated from a previously established focus at the tooth root by administration of a shocking dose of serum, and that localization of bacteria at the root ends could be accomplished by injecting the bacteria intravenously, while the shocking dose of serum was administered through the root canal

Sensitization may have been a factor in the production, as noted below, of

acute endocarditis and other lesions in animals by repeated intravenous inoculation of greening streptococci (111, 112 81). Indeed, in view of the ubiquity of these bacteria, the possible role of allergy in the production of lesions following even a single inoculation cannot be altogether dismissed. Rothbard and Angevine (113) have reported the development in rabbits of chronic lesions of the eye (choroiditis) with either viridans or hemolytic streptococci after repeated intravenous inoculation. With greening streptococci these results could not be obtained by a single injection or by repeated injection of killed bacteria or of bacterial extracts.

The relationship of these findings to disease in man remains to be clarified. Howell and Corrigan (114) and Nye and Segal (115) have reported that normal persons frequently show skin reactions when tested with filtrates of greening or non hemolytic streptococci. In view of the uniform presence of these bacteria on the mucous membranes, and of the data on transient bacteremias presented in the following section, such findings are not surprising. The implication that such sensitization in man may give rise to disease deserves to be kept open, but requires substantiation by additional research.

SUBACUTE BACTERIAL ("VIRIDANS") ENDOCARDITIS

The role of the greening and other non hemolytic streptococci in the etiology of subacute bacterial endocarditis, and of the mouth in its pathogenesis, has been well substantiated by an impressive group of investigations by many workers. In aggregate, these reports constitute a remarkably complete story of the causation of disease whose practical implications are only slowly achieving recognition. It seems worth presentation here in detail.

Herbitz (116) seems to have been the first to distinguish the less acute variety of endocarditis. Schottmuller (8) isolated *Str. viridans* from the blood in this disease during life, and later (117) called it "endocarditis lenta." Horder (83) was able to obtain streptococci of low virulence from the blood of many cases described either as "subacute" or "chronic" infective endocarditis, both of which appear to correspond with the disease under consideration. The term "subacute bacterial endocarditis" was applied by Libman and Celler in 1910 (118).

The etiological agent. The gonococcus, *Hemophilus influenzae* and occasionally other microorganisms are found in subacute endocarditis in a small percentage of cases, but the great majority of cases will greening or non hemolytic streptococci. The organisms found are usually of the alpha type (11). But *Str. faecalis* is frequently implicated and it now seems clear that the alpha type, based on the production of alpha and gamma reactions, [illegible] employed by the [illegible] of Avery and Hedrich (21). [illegible] of [illegible] and Sherman of *Str. faecalis* [illegible] Libman (119) [illegible] the streptococci [illegible] Howell (111) reported that [illegible] discovered [illegible] *faecalis* [illegible]

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The etiological agent The gonococcus, *Hemophilus influenzae* and occasionally other microorganisms are found in subacute endocarditis in a small percentage of cases, but the great majority of cases yield greening or non-hemolytic streptococci The organisms found are usually of the salivary type (14), but *Str fecalis* is frequently implicated and it now seems clear that the disease may be caused by a wide variety of alpha and gamma streptococci Horder (83), employing the classification of Andrewes and Horder (21), isolated 9 strains of *Str salivarius*, 6 strains of *Str anginosus* and 8 strains of *Str fecalis* from endocarditis Libman (119) found that most of the streptococci isolated from the disease produced greening on blood but that some were anhemolytic and some were slightly hemolytic Kriedler (111) reported that 13 strains of alpha streptococci from endocarditis could not be classified immunologically or by fermentation reactions Immune antibodies for the homologous strain were

found in the blood of all patients tested Among 20 strains isolated from endocarditis blood by Moran (120), 12 were *Str salivarius* according to Sherman's earlier criteria, 3 were *Str fecalis*, 2 were *Str zymogenes*, and 3 were peculiar, giving an alkaline reaction in milk and producing rods after cultivation Gunther (121) also reported marked differences in the biological characteristics of greening streptococci isolated from this disease Solowey (50), in the paper referred to above, studied 108 strains of viridans streptococci from subacute endocarditis and found them heterogeneous both immunologically and biochemically It seems particularly noteworthy that these 108 strains could not be distinguished as a group, even by the refined methods used by this worker, from 99 other strains that had been isolated from human throats and from extracted teeth There seems, in other words, to be no distinctive "pathogenic" variety or type of streptococcus responsible for this disease, it appears rather to be due to any of the varied types found on the mucous membranes

Predisposition Pre-existing cardiac disease is an especially important antecedent condition of subacute bacterial endocarditis According to White (122), old rheumatic valvular defects are present in about 80 per cent of instances and congenital defects in about 5 per cent, while in the remainder, the disease may develop on a previously undamaged heart Christian (123) found that rheumatic heart disease was present in 89 per cent of 150 consecutive adult cases of viridans endocarditis at Peter Bent Brigham Hospital The "determinative background" of subacute bacterial endocarditis, according to Christian, includes rheumatic heart disease in the absence of auricular fibrillation and of prior cardiac decompensation, in youths or young adults Keefer (124) considers the most vulnerable persons to be those with a history of rheumatic fever in childhood who have achieved good health and who have not had repeated rheumatic attacks, and states that aortic regurgitation, with or without mitral valvular disease, is a more important antecedent than mitral stenosis Von Glahn and Pappenheimer (125), however, have presented evidence that the disease develops on active, unhealed rheumatic lesions—although these may have existed in subclinical form for many years—rather than on old, scarred valves The commonest predisposing congenital defects—which are on the whole much less common antecedents than rheumatic defects—are congenitally bicuspid aortic valves, and patent ductus arteriosus According to Keefer, subacute bacterial endocarditis is exceedingly uncommon without a previous history of cardiac murmur Hedley (126) reported an extensive statistical analysis of 4653 cases of rheumatic heart disease, rheumatic fever, Sydenham's chorea, and subacute bacterial endocarditis involving 5921 admissions to Philadelphia hospitals during the five year period 1930 to 1934 Subacute bacterial endocarditis was the principal cause of 5 8 per cent of these admissions, and 64 5 per cent of the cases of this disease were regarded as superimposed on rheumatic heart disease It was noted that the peak of deaths from subacute bacterial endocarditis occurred during the third decade of life and that the average age at death was several years younger for cases on a basis of rheumatic heart disease than for those without such basis Gelfman and Levine (127) in a study of 34,023 autopsies at four Boston hospitals, found 453 with significant cardiac defects, of which 181

were more than 2 years old Of the latter, 30 (16 5 per cent), mainly in the second and third decades of life, had evidence of bacterial endocarditis

Animal experiments The Pathogenesis of Subacute Bacterial Endocarditis The principal evidence which makes it clear that non-hemolytic streptococci are the causative agents of subacute bacterial endocarditis is embodied in studies on the experimental reproduction of the disease in animals in which the postulates of Koch have been adequately fulfilled Horder (83) notes that in 1906–1907 he reported the production of "a condition of infective endocarditis in the rabbit by the intravenous injection of saprophytic streptococci from human saliva and feces " Rosenow (82) and Detweiler and Robinson (128) confirmed these findings It is of interest that the latter workers were able to produce endocarditis in rabbits with strains of greening streptococci obtained either from the blood of endocarditis patients or from the normal mouth MacNeal, Spence and Wasseen (112) also reported that recognizable inflammatory lesions of the endocardium were produced in 27 of 57 rabbits by repeated intravenous injections of large amounts of pure cultures of greening streptococci The lesions were said to resemble those of actively progressive (acute) endocarditis in man These findings have been confirmed by Loewe, Rosenblatt and Lederer (112a) Kriedler (111) produced lesions of the heart valves in rabbits with 5 strains of greening streptococci by repeated intravenous injection over a four month period, and also by repeated intracardiac inoculation with deliberate traumatization

Results more comparable to subacute bacterial endocarditis in man were obtained by Kinsella and Sherburne (129), who injured the aortic valve in dogs by inserting an instrument into the left carotid artery After the dogs had recovered, intravenous inoculations of greening streptococci resulted in the development of vegetations on the injured valve Kinsella and Muether reported their experiments in detail in 1938 (130) The aortic or mitral valve in dogs was traumatized by means of a long wire bent into a sharpened hook and passed down the carotid artery At least 30 days later a 24 hour blood broth culture of non-hemolytic streptococci, having little or no virulence for white mice, was injected intravenously Successful implantation occurred in several instances, bacterial vegetations developed on the heart valves and a persistent bacteremia appeared, with the blood culture count increasing progressively In these instances of successful implantation, death always resulted within 35 days The disease in these dogs was considered pathologically similar to subacute bacterial endocarditis in man Similar results in dogs were also obtained with streptococci in the presence of specific immune serum, and after immunization with dead streptococci These results, which indicate that antibodies to streptococci do not prevent the development of a fatal endocarditis, are in accord with the finding of circulating antibodies during the course of the disease in man (111, 124) Kinsella and Muether were also able to infect 6 of 11 operated dogs by feeding 10 cc of a 24 hour broth culture of streptococci, and 4 of 6 by inoculation through a stomach tube Dogs which did not become infected by these routes could later be infected by intravenous inoculation

Friedman, Katz, and Howell (93) reported that although the growth of green-

ing streptococci is inhibited by leucocytes, the organism grows luxuriantly on fibrin, an important component of the vegetations in subacute bacterial endocarditis Friedman (131) found that a fibrin mass *in vitro* is impermeable to colloidal particles and permits diffusion of small molecules only slowly and in inverse relation to the thickness of the fibrin mass The relative impermeability of such a fibrin mass was found to be augmented in the presence of serum It is noted that "an infected fibrin mass suspended in serum is the actual pathological picture encountered in subacute bacterial endocarditis" In experiments on dogs, Friedman, Katz and Howell (93) attempted to establish a parallel with the picture of viridans endocarditis in man A small perforated bakelite capsule, open at one end and filled with a blood agar culture of greening streptococci, was used to delay access of leucocytes to the bacteria The capsule, held at the closed end by a thread, was inserted in the abdominal aorta and fastened to the aortic wall so that the capsule floated free In 2 of 7 instances the capsule became covered with fibrin The organisms survived only in these animals and in one other Under these circumstances infection developed on the heart valves Persistence of the organisms in the capsule and on the valve was believed to depend on the fibrin mass, which provides an excellent medium for their growth and prevents the access of leucocytes

Subacute bacterial endocarditis thus seems to result from the implantation of greening or non-hemolytic streptococci on an abnormal or injured heart valve Grant, Wood and Jones (132) found that platelet thrombi tend to collect on the heart valves of animals as a result of injury, and that isolated thrombi are frequently found at autopsy on the heart valves in man Such thrombi nearly always occurred in areas known to be subject to infective endocarditis, and were believed to serve as peculiarly favorable areas for bacterial localization The immediate pathogenesis of subacute bacterial endocarditis thus seems clear The causative agents, found on the mucous membranes, ordinarily have little or no capacity to produce disease They have no distinctive capacity for tissue invasion, and lack other properties usually associated with virulence They are nevertheless enabled to produce fatal disease by a mechanism in which their own role seems to be essentially passive they become embedded in a mass of fibrin on a damaged or otherwise abnormal valve, the fibrin serving both as pabulum for their continued growth and as protection against the normal clearing mechanism of the blood, which would otherwise destroy them The friable streptococcal vegetations themselves, which continue to proliferate and from which fragments become detached as a result of the action of the heart, provide the source of emboli which in turn, by settling in and blocking the circulation of the skin, the spleen, the kidney, the brain and other organs, induce the progressive deterioration and eventual fatal outcome characteristic of the disease

The similarity of the causative agent to streptococci found on mucous membranes suggests an endogenous infection from such areas as the mouth or intestine This would require that the organisms gain access to the blood stream in order to reach the heart valves A considerable body of evidence indicates that such bacteremias occur and may serve as the exciting cause of subacute bacterial endocarditis

Transient bacteremias Many scattered reports have indicated that greening streptococci and other bacteria derived from the gastro-intestinal, upper respiratory or genito-urinary mucous membranes may be introduced into the blood during surgery or other manipulations Romer, for example, in 1913 (134) described the occurrence of a bacteremia following uterine curettage, and Brown (135) noted a similar phenomenon after appendectomy Siefert (136) reported that many different surgical operations were often followed by the transitory appearance of microorganisms in the blood stream, and that the proportion of positive blood cultures was higher after operations that involved considerable traumatization As early as 1920, Richards (137) observed that manipulations of arthritic joints may be followed by a bacteremia Lehmann (138) confirmed the observations of Romer (134) on bacteremia following uterine curettage, and Scott (139) and Barrington and Wright (140) noted a similar sequel of operations on the urinary tract In 1932, Richards (133) extended his earlier observations and reported that manual massage of several different infected areas was followed in many instances by the immediate appearance of bacteria in the cir-

TABLE 1

Recovery of microorganisms from the blood after manual massage of infected areas (After Richards (133))

AREA MASSAGED	NUMBER OF CASES	NUMBER OF POSITIVE BLOOD CULTURES	
		After massage	1 hour later
Joints	260	23	1
Tonsils	80	18	6
Gums	17	3	0
Prostates	6	1	1
Boils	13	5	0

culating blood, and that the blood culture was occasionally still positive one hour later Richards' results are summarized in table 1 Cultures from the "foci" yielded unidentified streptococci from tonsils and prostates, and from 18 of the 260 joints, all the boils yielded Staphylococcus aureus The mouths selected for study showed "definite inflammation" either in the gums or radiographically at the apices of the teeth No details are given in the report of the bacterial species found in the blood cultures

In 1930, Rushton (141) recorded that among 10 cases of subacute bacterial endocarditis at Guy's Hospital during 1922–1927, gross dental sepsis had been present in 17, and in less marked form in 7 others, 1 additional patients had given a history of dental extractions some time before the probable onset of endocarditis Rushton seems to have been the first to offer the concrete suggestion that there may be an important connection between "septic foci" in the mouth and the development of endocarditis in patients with previous cardiac lesions He noted that "the number of cases on record in which a dental cause can be assumed with confidence appears to be small," but perhaps only because dental conditions and history were frequently not mentioned in the case reports He also pointed

out that the delayed and insidious onset of subacute bacterial endocarditis may mask its possibly common connection with the teeth In the following year Abrahamson (142) reported 3 cases of subacute bacterial endocarditis, 2 of which developed after the extraction of teeth and the other after tonsillectomy, all with a previous history of cardiac disease

All these reports, however, seem to have attracted little attention, and it was only in 1935, when the report of Okell and Elliott (143) appeared, that the general question of the exciting causes of subacute bacterial endocarditis began to receive serious consideration The report of Okell and Elliott dealt with the prevalence of transient streptococcemia following tooth extraction, and it is of passing interest that, at this time, the authors discounted the importance of their findings in relation to subacute bacterial endocarditis In a subsequent report, however, Elliott (144) changed his mind on this question

In the original study (143), 138 subjects were divided into three groups in accordance with the severity of gingival disease and the number of teeth extracted, and cultures were made of blood drawn before operation, five minutes after operation, and a intervals thereafter Group I had severe gingival lesions and multiple extractions, group III had healthy gums and single extractions, and group II was intermediate Blood cultures made before operation yielded 12 positive results, 9 in groups I and II and 3 in group III Five minutes after operation, positive blood cultures were obtained from 75 per cent of group I (40 cases), from 70 per cent of group II (60 cases) and from 34 per cent of group III (38 cases) In the last group the concentration of bacteria per cc of blood was said to be lower than in the others Blood cultures taken from 10 minutes to 8 hours after operation were negative Greening streptococci were the organisms most frequently found in the positive cultures

While the very high values reported by Okell and Elliott have not been duplicated in later studies, the essential truth of their findings was quickly confirmed Round, Kirkpatrick and Hails (145) were able to recover *Staph aureus* in one instance, and *Str viridans* in another, from arm blood of 2 of 5 cases of pyorrhea immediately after the patients merely chewed mint candies for 10 minutes In 5 cases with other types of "oral sepsis" the results were negative, and in all 10, negative control cultures were obtained before chewing Similar results have been reported by Murray and Moosnick (146) Burket and Burn (147) recovered microorganisms from the blood, 10 minutes after extractions, in 16 9 per cent of 204 cases Diphtheroids, greening and non-hemolytic streptococci and *Staph aureus* were found most frequently They could not correlate the incidence of bacteremia with degree of "sepsis" or with operative trauma, and found that attempts to sterilize the gingival crevice with tincture of iodine before extraction were ineffectual These authors showed clearly that the microorganisms recovered from the circulating blood are in fact derived from the gingival area They painted a suspension of *Serratia marcescens* around the neck of the tooth before extraction, and recovered it subsequently in the blood in 18 out of 38 instances They also found, confirming Richards (133), that 5 minutes' digital massage of the gums of a patient with moderate pyorrhea was followed by

recovery of Staph aureus and greening streptococci from the blood 10 minutes later

In 1938, Elliott (148) recommended the use of small amounts of saponin in broth for blood culture to lyse the blood and prevent the action of the blood leucocytes on streptococci This method was said to make it possible to recover the organisms with increased sensitivity In a comparison of this method with the whole blood method, Elliott was able to obtain greening streptococci from the blood of a total of 39 out of 65 patients (60 per cent) immediately after dental extraction, 38 of these were positive with saponin as compared with 27 without saponin In a later paper, Elliott (144) reported that the movements of a tooth in its socket customarily induced with extraction forceps before actual removal of the tooth were in themselves sufficient to induce a transient bacteremia in patients with marked gum disease Positive blood cultures were obtained most consistently after such "rocking" of teeth with periodontal pockets, which were loose to begin with Bacteremia was also obtained, although somewhat less frequently, as a result of pre extraction movement of teeth with acute periapical infection but with healthy gingival tissues Palmer and Kempf (149) reported a 17 per cent incidence of bacteremias, predominantly greening streptococci, following extraction of one or two teeth The findings in this study have also been reported by Hopkins (150), it may be noted that the percentage value agrees closely with that of Burket and Burn (147) as given above Faillo (151) obtained positive blood cultures in 8 of 20 patients after tooth extractions, and Northrup and Crowley (152) have reported an incidence of 12 4 per cent positive cultures in 97 such cases

Most reports since 1935 on transient bacteremias following surgery or other manipulation have dealt with the teeth, and the data on other areas that are available do not make it possible to evaluate the relative importance of dental operations as compared with others Southworth and Flake (153) obtained 3 positive blood cultures before 22 tonsillectomies, and only 1 positive cultures after operation Millet and Van Eyck (154), who give references to additional reports on bacteremia following extra oral surgery, obtained positive blood cultures in 40 per cent of 100 cases of operation or curettage in chronic tonsillitis or enlarged adenoids in children Blood cultures before operation were uniformly sterile A wide variety of bacterial species was obtained in the postoperative cultures, with greening streptococci considerably less common than other types, such as *Gaffkya tetragena* and pneumococci The bacteremia never lasted more than one hour Additional references are also given by Burket (155) and by Keefer (121)

Importance of the teeth in transient bacteremias While the variations in these data are such as to prevent quantitative comparisons, the force of the findings as a whole seems inescapable It is plain that manipulation of an infected area in the body may be followed for a brief period by the appearance of microorganisms in the circulating blood Greening streptococci are by no means the only microorganisms to enter the blood stream in this way, but they do so commonly It appears that the probability of such a bacteremia may increase in proportion

to the concentration of bacteria at the manipulated site and to the degree or duration of the operative trauma And although precise data are lacking, the peculiar anatomy of the teeth and their supporting structures suggests that manipulations of the teeth or of the tissues around them may be of distinctive importance in the production of such bacteremias The periodontal membrane, a thin layer of connective tissue rich in elastic fibers and blood vessels, lies between two relatively unyielding walls, the tooth root and the alveolar bone At the coronal end this tissue is separated by a very thin mucous membrane from the free surface, which is never sterile, and is frequently the site of a massive accumulation of microorganisms The data suggest that in health, when the periodontal membrane and its overlying epithelium are intact, an effective barrier is maintained against the surface flora during functional movements in the area (e g , during mastication) In pyorrhea, however, the periodontal space becomes widened, the suspensory mechanism of the tooth is weakened, and the microbic accumulation has both increased greatly in amount and penetrated more deeply along the tooth root Under such conditions undue pressures such as may be induced by function or massage, abetted by abnormal mobility of the teeth, may pump bacteria from the surface into the intact and closely confined periodontal membrane and thus into the blood stream The tremendously increased pressures in the periodontal membrane that must attend the "rocking" movements of a tooth prior to its extraction seem to provide ample explanation for the aspiration of microorganisms into vascular tissue even though the gingival and periodontal areas be intact Such a view seems to have been suggested first by Fish and MacLean (156), who demonstrated streptococci in the blood and lymph spaces in the periodontal membrane and pulp of vital pyorrhetic teeth after extraction, and were able to prevent such infection by cauterization of the gingival area before extraction Tunnicliff and Hammond (157) and Kanner (158) have reported similar findings

Under ordinary circumstances a bacteremia induced as detailed above may be an event of no great importance, since the normal clearing mechanism of the blood eliminates the circulating microorganisms within a short time It is evident, on the other hand, that in a person with a previously damaged heart, perhaps with small fibrin masses already adherent to the abnormal valve surfaces, such a bacteremia may provide the opportunity for implantation of greening streptococci on the valve

Tooth extraction and subacute bacterial endocarditis In the years since attention was focused on this question, reports in increasing number have pointed to a relationship in time between antecedent tooth extraction (or, apparently less commonly, tonsillectomy) and subsequent endocarditis It has been noted that Rushton (141) and Abrahamson (142) were among the first to report such cases Additional cases have been reported by Bernstein (159), Weiss (160), Lamb (161), Feldman and Trace (162), Elliott (144), Sale (163), Palmer and Kempf (149), Paquin (164), Budnitz, Nizel and Berg (165), Geiger (166), and others Some of these are reports of single cases while others report multiple cases Elliott (144), for example, gives details of 13 cases of subacute bacterial endocarditis in persons

with preceding cardiac abnormality, all of which seemed to follow directly, within a few days or a few weeks, after extractions which were usually multiple and usually in "septic" mouths Budnitz, Nizel and Berg (165) state that Kelson found a 10 per cent incidence of recent dental surgery in 250 cases of subacute bacterial endocarditis at Massachusetts General Hospital and later, in 500 additional cases presumably with more complete records, an incidence of 25 per cent Geiger (166) notes that,

"in 50 proved cases of this disease [subacute bacterial endocarditis] drawn at random from the history files of the New Haven Hospital, the symptomatic beginning of the fatal infection was specifically mentioned in 12 instances as closely following extractions In 5 others, the suspicion of invasion from a dental focus was suggested by the physician's notation of 'recent dental work' in one, 'abscessed teeth' in another, 'extreme pyorrhea' in a third, and 'miserable condition of teeth' in two others In many of the case histories, there was no statement concerning the teeth or recent extractions, and perhaps specific inquiry concerning this detail was overlooked "

It is notorious that dental examinations and records in hospital cases are often grossly inadequate The mouth, as the physician sees it, is too often only a collection of blurred objects that block a clear view of the throat

Therapy Before the advent of sulfonamide therapy subacute bacterial endocarditis was considered invariably fatal Since that time there have been well authenticated cases of recovery (see Smith, Sauls and Stone (167)), but the number of cured cases continues to be very small Both viridans streptococci and the enterococci have been found sensitive to the sulfonamides *in vitro* (168, 169, 170) Experimental viridans endocarditis in dogs has been successfully treated with sulfanilamide (130), and in fully developed cases of subacute bacterial endocarditis in man, sulfonamide therapy has had an observable effect: "the blood became sterile and remained so throughout 33 days of treatment until the patient's death" (168) Friedman (131) showed that the fibrin-platelet vegetations in which the streptococci proliferate are relatively impermeable, and advocated the use of heparin in conjunction with sulfonamides with a view to dissolution of the fibrin Although such combined therapy has had some slight success in other hands (171), Friedman, Selzer and MacLean (170) themselves found it ineffective in clinical trials More recently Katz and Elek (171a) reported completely negative results with heparin combined with either sulfonamides or sulfonamides and intensive arsenotherapy Penicillin alone in large amounts has likewise been generally ineffective (171c) Loewe, Rosenblatt, Greene and Russell (171b), on the other hand, have described uniformly successful sterilization of the blood and clinical improvement in seven cases treated with heparin combined with penicillin Friedman and his co workers (170) had found that the sulfonamide drugs were very effective experimentally, both *in vitro* and *in vivo*, provided that the inoculum was small and that the growth had not been allowed to progress too far, a delay of as little as six hours prevented sterilization Successful treatment with these drugs would therefore seem to depend directly on very early diagnosis and institution of intensive chemotherapy before the infected vegetations have become too large, as Christian (172) has

pointed out In a study of 150 patients Christian reported that the earliest symptoms were, in decreasing order of frequency, (a) malaise and fever (in 52 6 per cent at onset, and in 71 3 per cent at onset or in the early days of the disease), (b) joint or muscle pains (in 42 per cent, at or near onset), and (c) nausea or loss of appetite (in 16 per cent, at or following onset) He recommended that, with a history of chronic valvular or congenital heart disease, such symptoms, persisting more than one week without definite evidence of other disease, indicate a high probability of subacute bacterial endocarditis To this list we may add, as confirmatory indications, the presence of pyorrhea, or a history of dental or other surgery within several weeks or months of the onset

Prevention The outlook for successful prevention of this disease, now that the essential facts of its pathogenesis seem clear, should be somewhat brighter than the prospects for effective therapy Prevention, however, here as elsewhere, is not easy to apply, and suffers from a lack of that dramatic or seemingly miraculous quality which often surrounds a successful cure Prevention seems negative, its effects on the individual may be inapparent or undemonstrable, and since it may require long sustained efforts, its value may be difficult to appreciate Such long range prevention seems most promising in this instance, but shorter range measures have also been suggested

Subacute bacterial endocarditis is evidently a *secondary* or derived process Its occurrence depends upon such antecedent maladies as rheumatic or other heart disease, and on impairments of other body areas, like the mouth, which harbor non-hemolytic streptococci At long range the prevention of subacute bacterial endocarditis therefore implies the prevention of these antecedent diseases A discussion of the prevention of heart disease in general is not within the scope of this review As for the prevention of mouth infections, while the means toward this end have not yet been attained in aggregate, there is much that can be done effectively for the individual patient These means are largely the dentist's responsibility, but it is obvious that he needs the co-operation of the physician in order to apply them For example, all patients with heart disease in early life, in particular with rheumatic heart disease, should be advised by the physician that unremitting dental care is more necessary for them than for others No fully guaranteed means for the prevention of dental caries can yet be offered, but early decay can be detected and effectively arrested, thereby preventing infections of pulp and periapical areas Some of the causes of gingival and periodontal disease are still obscure, but neglect is at least an aggravating factor in their causation, and suitable care can retard and minimize their effects where it cannot abolish them entirely

At shorter range the problem becomes one of the prevention or prompt control of bacteremias following dental extractions or other operative procedures in infected areas in patients with cardiac disease It would seem elementary to suggest that tooth extractions or other oral surgery should never be undertaken without a general physical examination of the patient, and perhaps the time will come when a general medical workup of the patient will seem an indispensable prerequisite to dental treatment of any kind

Several procedures have been recommended and tried for the control of bacteremias following the extraction of teeth Feldman and Trace (162) have suggested that the patient with heart disease who is in poor health should be "built up" before undertaking operative work on mouth or throat Elliott (144) recommended the preoperative improvement of oral hygiene in such patients, and the avoidance of multiple extractions and of excessive manipulative traumatization during extraction Fish and MacLean (156) reported that pyorrhea pockets could be sterilized with a cautery so as to prevent aspiration of infection into the tissues during extraction This method deserves more extended trial As noted above, a less drastic sterilizing procedure—with tincture of iodine—was not found successful by Burket and Burn (147)

Pretreatment with sulfonamides has been widely recommended, and has apparently been instituted as routine practice in several clinics on empirical grounds The indications for such a practice are obvious, and it cannot be suggested that it be withheld from the cardiac patient, but it is to be hoped that adequate data on dosage and duration of treatment, and on possible ill effects both immediate and remote, will be accumulated on the basis of controlled experiment before the practice becomes universal It may be noted that sulfanilamide has been given in small daily doses over long periods for the prophylaxis of rheumatic fever, with apparent success (173) The development of hypersensitivity to sulfonamides, which might prejudice a later use of the drug under critical conditions, has also been recorded (174)

Data establishing the value of sulfonamides in the prevention of subacute bacterial endocarditis are not yet available Such data will not be easy to acquire, since the proportion of cases in which extraction of a tooth or other operations in a patient with cardiac disease is followed by a subacute endocarditis is not known, and since such operations are by no means invariably followed even by a bacteremia The prevalence of both sequelae in the case of tooth extraction would seem to vary not only with the condition of the patient, oral and cardiac, but also with the surgical methods employed by the individual practitioner No control prevalence of endocarditis, or even of bacteremia, is to be looked for in cardiac patients, but a control prevalence, under the conditions of the experiment, of bacteremia in patients with no heart disease must be provided as a basis for comparison of chemotherapeutic action Budnitz, Nizel and Berg (165), without such control, selected 27 patients with valvular or congenital heart disease at the Worcester City Hospital after consultation between cardiac and dental clinics, and gave them sulfapyridine, 1 gram initially and then 0 5 gram every 4 hours, except during sleep, for 6 or 7 consecutive days Dental surgery was done on the third or fourth day Blood cultures, in a medium containing p amino-benzoic acid to neutralize the inhibitory action of the drug (175), were sterile both immediately and 30 minutes after surgery, and neither subacute endocarditis nor other major untoward reactions developed Northrop and Crowley (152) studied a larger number of both normal and cardiac cases, and included an untreated control group The latter comprised 97 minor oral surgical operations Blood was taken before, immediately after, and again ten

minutes after operation. With a few doubtful exceptions which the authors believed were due to contamination, all cultures of blood taken before and ten minutes after operation were sterile In 12 instances (12.4 per cent) positive cultures were obtained from blood taken immediately after operation, excluding 3 additional instances attributed by the authors to contamination A total of 73 cases were given 1 gram each of sulfathiazole and sodium bicarbonate, beginning on the day before operation and repeated every four hours to within one or two hours before operation, the total sulfathiazole dosage being 6 grams Blood samples, taken as before, were planted both in plain broth and in broth containing p-aminobenzoic acid Cultures of blood taken before and ten minutes after operation were negative, but 7 patients in the group (9 6 per cent) yielded positive cultures immediately after operation. Determination of the blood sulfathiazole levels in these patients disclosed that five of the positive cultures were recovered from among 23 cases in which the blood concentration was less than 3 mg per cent, while the other two positive cultures were obtained from among 50 patients whose blood levels ranged from 3 to 5 6 mg per cent These findings are obviously insufficient to establish the value of such sulfonamide prophylaxis They suggest that larger dosages may be required, and emphasize the need for careful evaluation and control of any recommended procedure before it is accepted for routine use

SUMMARY

This paper is a review of the classification, characteristics, and pathogenicity of aerobic streptococci other than the "pyogenic" group, and deals particularly with the pathogenic relationships of the streptococci of the mouth The several members of the viridans, lactic and enterococcus groups are described and distinguished, and current attempts at a serological classification, particularly of the viridans group, are reviewed The metabolism of the streptococci is discussed under the headings of relation to oxygen, lactic acid production, and the nature of the green pigment produced from blood Interrelationships among the streptococci are considered with special reference to greening variants of hemolytic forms

The disease-producing powers of the non-hemolytic streptococci are discussed in terms of virulence factors in the organism and resistance factors in the host, with emphasis on the experimental production of lesions in animals with pure cultures It is pointed out that except for subacute bacterial endocarditis there is no convincing evidence that these streptococci ever play a primary role in disease Dental infections are given brief separate consideration, and the peculiar difficulties of bacteriological studies of the mouth, dependent upon the complexity of the oral flora and on the distinctive anatomical characteristics of the teeth and their supporting tissues, are described Data are also reviewed on the significance of bacterial allergy in the pathogenicity of the non-hemolytic streptococci.

Subacute bacterial endocarditis is discussed in detail It is brought out that the streptococci concerned in this disease apparently do not constitute a distinct

"pathogenic" variety, but are evidently those of the mucous membranes generally Clinical and experimental data are reviewed which indicate that subacute bacterial endocarditis results from the implantation of viridans streptococci or enterococci on an abnormal or injured heart valve, where a mass of fibrin, by serving as pabulum and protecting the organisms against the clearing mechanism of the blood, permits their continued proliferation The findings of many workers are given which indicate that a transient streptococcemia, which in persons with cardiac defects may provide the source of infection of the heart valves, is provoked by manipulation of or operation upon contaminated areas in or adjacent to mucous membranes which harbor these streptococci It is noted that although the dental and periodontal tissues are not unique as sources of such infection, their peculiar anatomy may lend special significance to them Numerous cases are cited in which subacute bacterial endocarditis is known to have followed operations on the mouth Finally, the means available for treatment and prevention of subacute bacterial endocarditis are reviewed, including an appraisal of the use of sulfonamides to control transient bacteremias following tooth extraction

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MALIGNANT INTERSTITIAL EMPHYSEMA OF THE LUNGS AND MEDIASTINUM AS AN IMPORTANT OCCULT COMPLICATION IN MANY RESPIRATORY DISEASES AND OTHER CONDITIONS AN INTERPRETATION OF THE CLINICAL LITERATURE[1] IN THE LIGHT OF LABORATORY EXPERIMENT

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I INTRODUCTION

A Malignant and Benign Pneumomediastinum

There has been in the last decade a marked increase in the number of recognized cases of pneumomediastinum There is no reason to believe that the condition is more frequent now than formerly The increase in the number of reported cases arises from improvement in diagnosis Many of the instances which have been reported have been benign, the patient recovered spontaneously There

has been, therefore, a tendency to regard air in the mediastinum as of no dire import, and to emphasize that the chief value in its recognition is to prevent the physician from making an unduly grave prognosis We would point out that, although this condition often is benign, yet it may sometimes be fatal, and the mistake of underestimating its implications is to be avoided

Benign pneumomediastinum differs from what we have chosen to term "malignant pneumomediastinum" not in kind, but merely in degree The conditions under which the benign form may become malignant are

(1) When pressure of air bubbles on the blood vessels and heart interferes with the circulation

(2) When, from massed air bubbles in the pulmonic interstitial tissue, there is a splinting of the lungs in the inspiratory position thus making further respiration progressively difficult or even impossible

(3) When the pressure in the mediastinum rises too high

(4) When the usual escape routes into the neck and retroperitoneum are not opened out

(5) When air escapes into *both* pleural cavities causing bilateral pneumothorax

(6) When a serious inflammatory condition exists in the lungs

(7) When cough is present creating a tension pneumothorax

(8) When the condition occurs as a sequel of atelectasis in the newborn The factors responsible for the appearance of benign pneumomediastinum are the same as those which are the forerunners of the malignant type, and will here be reviewed First, however, because of the tendency to view all cases of pneumomediastinum as "benign," we wish to quote a description of what we believe to have been malignant pneumomediastinum and pulmonary interstitial emphysema, and to show that air in the mediastinum is not always harmless, but may actually weight the scales in favor of death in patients who will recover from the primary disease, if pneumomediastinum does not develop

This quotation about to be given also serves to bring out one of the major characteristics of the malignant type of interstitial emphysema, namely, that its presence may be, indeed usually is, unrecognized The air is occult, hidden, trapped in connective tissues where it exerts its malignant effects upon blood vessels of lung and mediastinum and upon the heart itself It masquerades under symptoms that simulate heart disease (206) dyspnoea, cyanosis, anginoid pains, and falling blood pressure all tend to convince the physician that the patient's disease is cardiac in origin, and the true culprit is not even suspected As will be noted from the cases in the literature reviewed, the presence of air was usually not thought of, or the mode of its production was misinterpreted or it was not understood by the physician. Finally, in many cases the presence of air in the mediastinum and interstitial tissues of the lung has probably proved fatal

The account of Torrey and Grosh of patients with influenza in the 1918 epidemic well describes some of these cases They called the condition "acute bronchitic emphysema" or "pulmonary emphysema," but the description of the patients and some of the findings at autopsy leave little doubt in our minds that they were dealing with malignant pulmonary interstitial and mediastinal em-

physema They say, "The point which struck us here was the intense dyspnoea, with little cardiac disturbance, cyanosis, great air hunger, and erection of the chest fixed in a state of hyperinspiration, with only tidal air movement As the muscles of respiration failed, exitus occurred, a respiratory death, in contradistinction to the toxic circulatory or vasomotor death commonly seen in the early days of true pneumonia The pulse impressed us as being slowed as if under the influence of cardiac vagotonic inhibition, as in high pulmonary pressure Very soon the accessory muscles of respiration were the only effective ones giving a lift to the upper chest, already so distended that any gain in capacity was impossible Sternal tympany became more marked, assuming a box-like character Marked stasis of all the veins entering the chest and those drained by the superior vena cava was manifest Cyanosis became more profound and in the end stage there was an ashen lividity of the whole face and chest

"When in apparent respiratory *extremis*, frequently a patient would begin to complain of pains, substernal and in the jugular fossae, and crepitation would be noted in the subcutaneous tissue at the root of the neck, and immediate marked subjective relief was apparent, rapidly followed by a noticeable improvement in the respiratory excursion of the chest, and the most striking decrease in cyanosis and jugular distention . As the intrathoracic pressure was thus relieved these apparently moribund patients often went on to recovery.

"A number of patients dying in this early stage of emphysema came to autopsy The cause of death was evidently the mechanical obstruction of the return flow of the venous blood from the general circulation to the interior of the chest by the thoracic fixation interfering with the mass movement of the blood . The lungs of bronchitic emphysema showed a great similarity in gross pathology as well as in clinical findings The surface showed the rib markings and emphysematous bullae, which were plainly visible under the visceral pleura The emphysema was such that *the lungs could not be collapsed by pressure* The tissue, while apparently solid, was always found to be air-containing, floated in water Regarding treatment it must be said that no routine treatment was shown to be of value after the bronchitic emphysema was established "

These patients, described by Torrey and Grosh, were suffering, we believe, from interstitial air, air in the wrong place, undoubtedly (as we interpret it, from evidence later to be presented) in the tissues about the blood vessels, compressing them, so that even a good myocardium could not drive blood through their narrowed, or even obliterated channels, and also air in the connective tissue septa, ballooning up the lungs, and preventing their collapse in expiration: air in the lung, true enough, but inaccessible to the capillary net about the alveoli because it was trapped in connective tissue and could not escape, air in the mediastinum, compressing the vessels there; air over and about the pericardium, interfering with the action of the heart To paraphrase Coleridge

"Air, air, everywhere,
"But not a whiff to breathe "

One would have thought that the witnessing of sudden and obviously material relief coincidental with the appearance of subcutaneous emphysema would have

suggested that the escape of air from somewhere was salutary, and that "somewhere" could hardly have been other than the mediastinum Thus, tapping of the mediastinum, by the introduction of a hollow needle, might well have suggested itself, a technique now used in newborn children with pneumomediastinum for withdrawing air (116, 117) Trocar needles have been inserted into the subcutaneous air pockets to permit of the escape of air (205) The last-mentioned procedure may give some indirect additional relief from the pressure in the mediastinum in cases in which it has already been materially relieved by escape of air into the neck

It is not to be wondered at that pathologists and clinicians alike failed to appreciate even the existence, much less the importance, of the underlying condition of widespread interstitial emphysema in these cases, particularly that of the lung and mediastinum, because the usual methods of examination of post-mortem tissues are inadequate in these particular cases, since they do not favor the disclosure of the aberrant air The long delay which usually takes place between death and the performing of an autopsy leads to a disappearance of much of the visible air from the tissues During the handling of the parts at autopsy many of the bubbles burst, leaving no trace of the air that once gave them shape Then, too, the usual methods of fixation of the lung after removal from the chest make for retraction of the connective tissues and serve still further to squeeze the air out of them Not until one has looked upon such a lung fixed in normal shape and size soon after the death of the animal or person can one gain a real comprehension of the exact morphology of pulmonic interstitial emphysema

The circulatory and respiratory impediments arising from interstitial emphysema of the lungs and mediastinum are so serious and frequent as to make it desirable to give this clinical condition a name, and thus it is referred to as "airblock" Already one of us has written (196) "The condition arising from interference of air in the lung, mediastinum, and extensions therefrom with the vital functions of respiration and circulation may be termed 'airblock'", and we shall use this term, as here defined, in this paper

It is well to note that there are two malign elements at work in airblock, (1) the interference with the circulation, particularly the pulmonary circulation, arising from compression, by air bubbles of varying size, of the pulmonary arteries and veins, the great vessels of the mediastinum, the heart, and also the vessels carrying blood into, or out of, the mediastinum, (2) the interference with the respiratory movements of the lung on account of the locking, or splinting, action of the air in the interstitial tissue of the lung, in which inflation and deflation are alike inhibited These elements always occur together with varying emphasis on one or other of the two factors, and it is difficult to separate out their specific clinical manifestations, so that it seems best to merge them together into the general syndrome covered by the term "airblock"

As an aid to the interpretation of the factors at work in introducing air into these usually airless regions, the following review is presented We shall first consider briefly the explanation of pulmonic interstitial emphysema or PIE[2] al-

[2] To save space, these symbols will be used throughout the text

ready recorded in the literature (188, 189, 190, 194), emphasizing its importance not only in deranging function within the lungs, but also its action in giving rise directly to pneumomediastinum or PM, to the so-called "pneumopericardium" (in reality, in the majority of cases, an anterior pneumomediastinum or pneumoprecordium, or PPC), to pneumoretroperitoneum, or PRP, and even pneumoperitoneum, or PP, to pneumothorax, or PT, and to subcutaneous emphysema, or SE, of the root of the neck, axillae, groin and adjoining regions

B Anatomical Considerations

How does air get from the lung into the mediastinum, (for in the majority of instances it is obvious that the source is the lung)? Under what conditions does air escape? These two questions must be answered before we can understand the cause and effects of air in the mediastinum and the interstitial tissues of the lung, and thus adequately answer the third question, "How can the presence of air outside the alveoli prove fatal?"

The Bronchial Tree in Respiration To answer these two questions the dynamics of the bronchial tree must be visualized The bronchial tree is divided into two parts, the *conducting*, consisting of trachea, bronchi and bronchioles, and the combined *conducting and respiratory*, consisting of respiratory bronchioles, alveolar ducts, sacs and alveoli Although the respiratory element predominates at the periphery of the lung, since large bronchi and bronchioles are lacking here, it must be remembered that expansion takes place *throughout the whole lung*, since alveoli surround the bronchi and their divisions, as well as the large vessels, from the hilum of the lung outwards

This brings us to the important division of alveoli into two types (a) those which have their bases lying between other alveoli ("partitional" type), and (b) those whose bases rest against some structure other than adjoining alveoli ("Marginal" or "non-partitional "type) This latter class, whose bases abut upon bronchi, bronchioles, blood vessels, connective tissue septa or pleura, is alone concerned in the production of pulmonary interstitial emphysema (PIE), and its sequels, pneumomediastinum (PM), etc Pores exist between the alveoli of the first type, so that air can pass from one alveolus to an adjoining one, but when air escapes from the base of the second type of alveolus, it makes its way only into one place, the underlying connective tissue This is the first step in the production of PIE, and later PM How can these one-sided alveoli be made to rupture? To answer this we must again resort to an explanation of the occurrences in normal respiration

When air is drawn into the bronchial tree by the enlargement of the thorax, through the action of the muscles of inspiration, the alveoli of the lung expand As the marginal alveoli abutting upon the bronchi and blood vessels of the lung open up, the structure against which they rest undergoes, of necessity, a simultaneous change, the bronchus or the vessel, as the case may be, elongates, and at the same time increases in diameter (183, 184, 197) Thus the stroma pull of the expanding lung opens the vascular bed for increased blood flow during the in-

spiratory phase when it is most needed, and opens the airway for greater inflow of air

When the end of inspiration is reached, and the chest wall begins to collapse against the expanded lung, the bronchial and vascular rays are shortened and narrowed as the alveoli surrounding them expel some of their air content In normal respiration, the expansion and elongation of the broncho-vascular rays takes place, *pari passu*, with the expansion of the alveoli whose bases make tunnels through which the broncho-vascular rays run If respiration be reduced, as in sleep, the expansion of the alveoli is lessened at the same time that the respiratory excursion of the lungs, and hence of the broncho-vascular rays, is correspondingly decreased, and less air and less blood enter the lung If respiration be increased in depth, as in exercise, the reverse takes place, and with the augmented expansion of alveoli, greater elongation and widening of the broncho-vascular rays is evident The space between the alveolar bases and the bronchial or vessel lumen, which is in reality the connective tissue sheath of these bronchi and vessels, stays constant in volume, because its interstices are filled with non-expansile tissue fluid This space forms a thinned rim of a larger circle in inspiration, a thickened rim of a smaller circle in expiration (Fig 1), but throughout the respiratory cycle, its *volume* remains constant

C · Pressure Gradient Factor in PIE

Can this normal relationship between alveolus and underlying connective tissue be altered so as to produce a rupture of the alveolus with escape of air into the tissue beneath? It should be emphasized that rupture must be through an alveolar base Rupture of the sides, even if it occurred, would lead only into neighboring alveolar spaces

Distention of Alveoli Factor "A" If the alveoli are overdistended with air, that is, in a state of hyperinflation, what may occur? In the alveoli that have their bases resting upon a bronchus or bronchiole or upon other alveoli, nothing happens, because the same excess quantity of air that distends an alveolus is distending the rest of the airway, and the bronchial lumen or adjoining alveoli are overexpanded also The conditions of normal inspiration are present merely to an exaggerated degree, and although the sheath of the bronchus may be narrowed even more than usual, the pressure relations are constant between air in the alveolus and in the bronchus

But what of the alveoli bordering upon blood vessels? Normally, the alveoli are hyperexpanded when the depth of respiration is greater than usual Under these conditions, the amount of blood in the pulmonary arteries and veins is correspondingly increased If, however, the heart cannot keep pace by pumping enough blood into the pulmonary arteries to expand the arterial lumen sufficiently, or if the return venous flow to the right heart is retarded, then the alveoli around the vessels are overexpanded, but the vessel lumen is not correspondingly widened, and a pressure gradient is created between the alveoli and

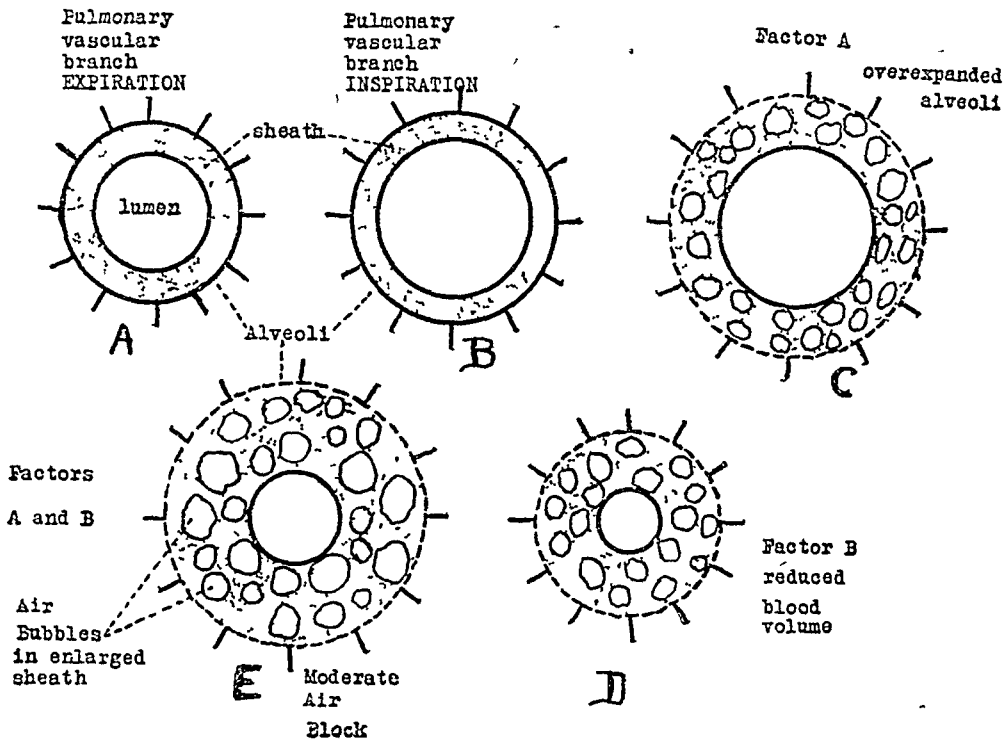

FIG 1 In this figure the outer circle represents the bases of a ring of 12 alveoli around a blood vessel The sides of the alveoli radiate like spokes of a wheel The inner circle represents the endothelial wall of a blood vessel The stippled area between the two circles is the sheath of the blood vessel

A This represents the conditions at the end of quiet expiration

B This is the same vessel and its surrounding alveoli at the end of normal inspiration The bases of the alveoli are stretched, the circumference of the vessel is greater as more blood flows into the lungs, but the *volume* of the sheath remains constant It is a thinner rim around a wider lumen than in A

C This represents the conditions in overinflation The inner circle of vessel wall is the same as in B, being dilated as in normal inspiration, but the alveoli are much distended, so that the circumference of their bases is much greater This puts a tension on the sheath between overexpanded outer circle and normally expanded inner circle The alveolar bases break as shown by the dotted lines, and air escapes from the alveoli into the sheath as shown by the large bubbles This factor of overinflation we have called Factor A The secondary compression of the vessels induced by the escaped air is not shown in this figure, lest it be confused with Factor B in the next part of the figure

D A strain may be put upon the sheath of the vessel creating a pressure gradient by making the inner circle smaller instead of the outer circle larger This means a reduction in the amount of blood going through the pulmonary vessels so that the lumen is smaller As forced expiration against obstruction is accompanied by the damming back of blood on the systemic venous side, the outer circle of alveoli is a little smaller than in normal inspiration, but not as small as in expiration where the air can escape normally from the mouth The inner circle is much smaller than in A Again a gradient is created, and air enters the sheath This we have called Factor B

E Factors A and B may be combined, the alveoli may be overdistended, and the blood vessel caliber lessened This heightens the gradient and induces rupture more readily Such an accident would occur when men escaping from a submarine ascend to the surface and hold their breath, thus lessening the pressure on the chest and permitting of expansion, without equalizing the pressure in the alveoli with that on the chest Holding the breath causes venous stagnation, with less blood entering the pulmonary vessels hence lessening of the vessel lumen This combines Factors A and B For a discussion of clinical conditions involving Factors A and B and combinations of these with increased intraalveolar pressure, see text

the sheath The alveolar bases are trying to expand, that is, to enlarge the outer rim of the vessel sheath, and the sheath does not follow owing to the inadequate expansion of the vessel lumen Rupture of the bases takes place, and air flows into the vascular sheath (Fig 1, C)

This factor of overinflation of alveoli, without corresponding expansion of the vascular lumen, permitting of the establishment of a pressure gradient from alveolus to vascular sheath we have termed Factor A (195)

The bases of alveoli which rest upon connective tissue septa may also rupture since their expansion may be greater than that of the underlying connective tissue, and air may get into the septa in this way

Reduction in Caliber of Pulmonary Vessels Factor B Since the essential factor in the production of PIE is the establishment of a downward pressure gradient from alveolus to the vascular sheath permitting of leakage of air from ruptured alveoli, we see that this pressure gradient can arise in two ways The first is by the enlargement of the outer circle of alveolar bases without a corresponding enlargement of the inner circle of vascular lumen, which we have just described and called Factor A *The second way is by a narrowing of the inner circle, or vessel caliber, without a corresponding diminution in the outer circle This we term Factor B* The end result is the same, namely, a pressure gradient from air in the alveolus to the vascular sheath beneath, although the circumstances creating the pressure gradient would differ widely in the two instances (See Fig 1, D) Circumstances might arise in which there was a combination of both of these factors, thus enhancing the opportunities for the escape of air into the vascular sheath (Fig 1, E)

Increased Intra-alveolar Pressure The pressure inside the alveoli might be increased above the atmospheric pressure to the point at which rupture might be induced Again the pressure inside the bronchi and the alveoli would be the same, and there would be no pressure gradient between the two, but the pressure in the vascular sheath might not be sufficient to withstand the pressure inside the alveolus, and rupture might occur In most cases, at least, increased pressure in the alveoli is accompanied either by overinflation, or by reduction in vessel caliber, so that the rupture in these cases would be associated with either Factor A or B, or both

To sum up PIE occurs because there is created a set of conditions which removes the support of, or weakens, the marginal perivascular alveolar bases, these conditions are caused by the inability of the fluid-rich tissues of the sheath to expand and so enlarge the space between alveolar bases and vessel wall This results in a reduced pressure in the sheath followed by a break in the alveolar bases, and escape of air from alveoli to vascular sheaths Continuance of these conditions means continuance of air leakage, and, depending upon the amount of the latter, various trains of symptoms may be elicited Pneumomediastinum is caused by the fact that the air tends to follow the path of least resistance, which is determined by the lengthening and shortening of the broncho-vascular rays already described, and makes its way toward the hilus

Having discussed the modes of production of PIE, that is, having answered the question as to how alveoli can be made to rupture with escape of air, we shall briefly recount the experiments which led to the above conception, and then show how in clinical cases the essential conditions may parallel those found in the experiments

D Results of Experimental Work in Which Local Overinflation Occurs

A brief review of the experimental work in which local overinflation of the lung substance occurred, as demonstrated by X-rays, with compensatory volume diminution in other regions, is now given This will serve as a basis for the interpretation of the clinical condition of PIE

In these experiments (188), air was blown into the right lower lobe of the lung of the living anesthetized cat by way of a catheter terminating in the main bronchus. Double pneumothorax was produced In searching for the cause of this, it was concluded that the first step was air passing through numerous minute ruptures in the strained bases of the alveoli of the overinflated region into the underlying vascular sheaths The air bubbles, at first very minute, moved along the vascular sheaths, coalescing and gaining in size. This streaming of air through the pulmonic interstitium reminded one of the flow of a river that ever increases in size by addition of new tributaries as it proceeds on its course Reaching the root of the lung the train of air bubbles passed into and distended the mediastinum With continued insufflation an actual overflow into the retroperitoneum, anterior mediastinum and subcutaneous tissues of the root of the neck and axillae occurred In extreme cases the mediastinal wall ruptured producing a pneumothorax, which in cats was always bilateral

These ruptures in the alveolar bases are not visible in ordinary histological sections, but must be demonstrated by a special technic (191) After the ruptures had been produced, hot gelatine containing minute carmine grains was introduced through the same catheter, left *in situ*, which had admitted the air In sections of the injected part of the lung the gelatine was mixed with air bubbles in the vascular sheaths, and streams of carmine granules led from definite points on the bordering alveolar bases into the gelatine in the sheaths These streams marked the points of larger ruptures Again, heaps of carmine granules on the air side of alveolar bases marked the positions where the grains had been filtered out as the gelatine passed through the ruptures too minute to be traversed by the grains. When the air pressure in the alveoli was great, it ruptured the capillaries and then red blood cells were found in the vascular sheaths This is of interest in connection with the manner in which hemothorax is produced in some cases

This conception gives a new significance to PIE The air in the living animal or patient affected with this condition is often not static but moving along toward the mediastinum Its presence (193) interferes with the pulmonic as well as with the cardiac circulation and leads to other disadvantages later to be referred to

Route of Air from Alveoli to Mediastinum Careful study did not reveal any air bubbles in the sheaths of the bronchial tree in these animals, the reason probably

being that these tubes, under the conditions of the experiments, have a pressure of air within them equal to that in the surrounding alveoli, both being distended by the insufflated air

The lymphatics have been suggested as a highway for air from alveoli to mediastinum (30), and it is quite possible that these structures in the vascular sheaths may be torn across and even invaded by air, but the air does not make much use, if any, of the lymphatics as a channel in passing toward the hilus They are too small to accommodate the large bubbles which may be an inch across at the hilus and in the mediastinum Polak and Adams stated that in similar experiments neither the lymphatics of the lung nor the thoracic duct contains air

Air was not found in the septa between the secondary lobules of the lungs of the cat, since in this animal these structures are relatively light It was found here in a human lung (94) and also in the overinflated calf lung (196) in which the septa are marked Subpleural blebs were not noted in the cat, though these have been reported in clinical cases, following influenza (157, 330) Air probably gained entry into these subpleural blebs by rupture of the alveoli under the pleura, or by dissection along the venous sheaths as they run to the pleura It is unlikely that air passed from these blebs beneath the visceral pleura around to the hilus, as some writers have intimated (157) When the air in the blebs finds a highway to the hilus it probably is by way of the intrapulmonary *vascular* sheaths, as was also noted by Berkley and Coffen, in their cases of influenza This answers the second question as to how this escaped air reaches the mediastinum

E Results of Experimental Work in Which General Overinflation Occurs

Excised lungs from newly-killed calves were inflated by air forced into the cannulated trachea under pressure (196) When the lungs had become distended to the maximum it was noticed that air was escaping from the vascular sheaths at the root region, as fast as it was injected into the trachea Air also infiltrated the connective tissue of the interlobular septa of the lung, giving the surface a curious mosaic appearance When the tube was removed from the trachea the lungs did not collapse to their initial volume, affording a striking contrast between the dimensions of the fresh, collapsed lungs and those of the end result of this inflation process The air trapped in the septa and about the vessels acted as a splint, preventing the egress of air and the collapse of the lung The bubbles of air about the pulmonary vessels had so compressed their lumina that injection of the pulmonary vein under a pressure of three feet of water was impossible

If such a condition existed in the living animal the ebb and flow of air would at first be impeded, and the chest would become increasingly fixed in the inspiratory position Each succeeding breath would drive more air into the interstitium of the lung, thus further compressing the pulmonary vessels and also making the next act of expiration still less effective Finally the animal, showing marked dyspnoea and cyanosis, would die with the chest in the position of maximum inspiration The descriptions by Torrey and Grosh, already presented, of some of

the patients suffering from influenza and pneumonia, correspond exactly to that just given There is no doubt in our minds that airblock was a very important factor in the cause of death in these cases. This answers the third question as to how this escaped air can prove fatal

The same course of events is not observed in all animals when subjected to general overinflation, and the difference would seem to depend in part, at least, upon the degree of development of connective tissue in the septa and beneath the pleura Thus when three rabbits (192), (in which the connective tissue is not stout) were subjected to general overinflation of the lung by air blown into the cannulated trachea, the degree of PIE was much less than it was in calf lungs, where the connective tissue is well developed In two of the three there was a definite rupture of the lung itself through which air escaped into the pleural cavity. This tear occurred in each case in the posterior aspect of the left lower lobe, and would seem to occur there because the lung lacks support at this point Elsewhere the lung is splinted by the thoracic cage, or by the diaphragm supported by the firm liver on the right On the left, however, the diaphragm can be pushed down, displacing the stomach, and so offering little support to the hyperexpanded lung Pneumothorax in these animals was caused, apparently, not so much by the rupture of the mediastinal pleura after the appearance of PM, but by a blow-out in the lung lobe In the third rabbit, there was no tear, but the lung was discolored and soft in the posterior aspect of the lower left lobe at a point exactly corresponding to the tear in the lungs of the other animals Thoracic wall (external) support is thus of importance, in addition to stroma (internal) support Further experiments will be carried out to determine the critical pressure in the rabbit at which an actual rupture of the lung takes place

Kelman, and Joannides and Tsoulos have produced general overinflation of the lung without describing PIE in detail They have, however, described PM, PPC, PRP, SE, and, in the case of the latter two authors, PT Therefore, it is probable that the first step in the dispersion of air from its normal container into the connective tissue of the lung, namely, escape into the vascular sheaths, had been taken in their animals, but was not mentioned Jessup stated that Kelman observed peribronchial and *perivascular* interstitial emphysema, but at no place in her article were we able to find the latter statement She said "First a vesicular emphysema is produced Increased intrapulmonary pressure causes rupture of some of the superficial distended air vesicles and there is an escape of air underneath the visceral pleura, which is rather firm The air finds less resistance in escaping underneath the pleura toward the hilus than to break through it" It would appear, then, that she considered the route of the escaped air to be around the visceral pleura on the surface of the lung to the hilus This is further borne out by her statement that the ruptured alveoli are all at the surface where they have little support rather than in the depths of the lung The experiments demonstrating the site of the ruptures (191) show that the break-through is not only in the alveoli under the pleura, but also in alveoli throughout the depths of the lung, wherever they are around blood vessels

In all of these experiments, the overinflation was accomplished by blowing air

or gas into the lungs under increased pressure It might be considered that it was the latter factor which caused the rupture Griffin (113), however, produced general overinflation uncomplicated by increased pressure within the alveoli He placed dogs, in whom a tracheotomy tube extended from the trachea to the outside air, inside a decompression chamber, and lowered the pressure PIE, PM, PT, PRP and SE all occurred Inflation alone seems to be responsible for this occurrence It must be pointed out, however, that although the pressure in the alveoli in these dogs was atmospheric, it was *relatively increased* as compared with the pressure on the thorax Hence the relationship between pressure in the alveoli to pressure on the chest was the same as in those experiments in which general overinflation was accompanied by hyperatmospheric pressure, namely, the pressure in the alveoli was abnormally high as compared with the atmospheric pressure on the chest wall

Polak and Adams found that the alveoli would withstand a great increase in pressure, provided that the lung could not overexpand They bandaged the chests of their dogs tightly to prevent the air, which was blown in, from ballooning out the lungs and the chest wall, and found that under these circumstances the alveoli did not rupture even with relatively high pressures It is obvious that the bandaging of the chest increased the resistance to expansion of the chest wall, thus increasing the supporting pressure As the internal intra alveolar pressure was raised, the supporting pressure on the outside of the chest was also increased The work of Griffin and of Polak and Adams confirms the statement made earlier in this paper, namely, that the essential cause of PIE is the establishment of a *pressure gradient* from alveolus to sheath When the alveoli lack support, they rupture, and the lack of support is caused by diminution of pressure in the surrounding perivascular tissues The alveoli can withstand high pressures inside them, if the pressure outside is equally high, they can be made to rupture at atmospheric pressure, if the surrounding (supporting) pressures are too low It is the steepness of the gradient that is responsible, not the levels between which the gradient lies This pressure gradient arises through the operation of the following factors, either alone or in combination, (1) overinflation, (2) reduction in blood flow throughout the pulmonary vessels, (3) increased intra-alveolar tension General overinflation alone in man does not usually produce alveolar rupture When rupture does occur in these cases, increased intra-alveolar pressure or decrease in vessel caliber or both will be found as accompaniments in most instances

II CLINICAL CASES OF PIE AND ITS SEQUELAE

A Involving Factor A

1 Cases in which a Pressure Gradient is Produced by Local Overinflation of the Lung Having shown that overinflation of alveoli of the lung without adequate basal support may produce PIE we will now present evidence, deduced from clinical records of cases of local and of general overinflation, which indicates that PIE and its sequels have sometimes been present Of course, the clinical records have not stated (in the majority of cases, at least) that PIE was

present, nor have they even interpreted the sequelae as dependent upon PIE. Not all such cases were fatal, of course, and in some that were fatal, the primary disease from which the patient suffered would be sufficient to provide a plausible explanation of the cause of death In other instances the records indicate that the patient was recovering from the primary disease, when the sudden onset of PIE and PM, as revealed by the symptoms, turned the balance in favor of death Although PM in itself may be fatal through pressure on the great vessels and heart, the very fact that a rupture of the mediastinal pleura to produce PT, especially bilateral PT, is always possible when PM is present, should induce us to avoid treating so-called spontaneous PM too lightly

How does local overinflation occur in the human patient?

Because of the anatomical structure of the thoracic cavity, diminution in the size of any part of the lung must be compensated for in one of several ways (1) Elevation of the diaphragm on the atelectatic side, (2) immobilization with or without retraction of the chest wall on the affected side, (3) presence of liquid or air in the pleural cavity, (4) overexpansion of some part of the lung The first two factors can compensate only to a limited degree, and the third is not always present Hence atelectasis of any amount is frequently accompanied by compensatory alveolar ectasia. The smaller the area of atelectasis the more localized often is the area of compensatory overdistention, so that it seems quite possible for air leakage to occur from a comparatively limited area of compensatory alveolar ectasia

A word must be said here as to alveolar pores, the so-called "pores of Kohn" If the area of beginning atelectasis is small, and if no pneumonitic reaction occurs to produce an exudate closing the pores of the alveolar wall (185, 186, 187, 309) air may inflate it through the pores from adjoining aerated regions, thus expanding it and preventing the hyperinflation of the surrounding region, and its possible consequence, PIE If, on the other hand, the atelectasis occurs in an entire lobe where pores cannot permit of entrance of air, there being no pores between lobes, or if an exudate covers and fills the pores, so preventing the admission of air from adjoining regions, then hyperinflation occurs and, depending upon its extent and the natural resistance of the alveolar walls, PIE may result Subdivisions of lobes may be similarly blocked off because of their being separated by septa which contain no pores, this is conspicuously true in the bovines

Atelectasis Any condition which induces atelectasis may initiate PIE Thus, obstruction of a bronchus by a growth in the lumen, or by pressure of a growth from without, by a foreign body in the esophagus or bronchus, by mucus in the airway which cannot be expelled, by constriction of a bronchus from congenital or other causes or failure of the atelectatic lung of the newborn to expand, etc , may be the beginning of the train of events ending in PIE This danger from atelectasis, however, would seem to depend on suddenness of production

Many of the recorded clinical cases in which PIE or some of its more extensive manifestations have occurred, are those in which pneumonic inflammatory reactions have blocked part of the airway, with subsequent absorption of air, and diminution in size of the corresponding area of the lung Thus pneumonia, influenza, diphtheria, measles, tuberculosis, silicosis, smallpox, etc , have been re-

ported as accompanied by PM, SE, PT, PPC, etc The atelectasis may not always be demonstrable, or the roentgenogram may be taken too late to show it, although its earlier presence initiated the events which culminated in PIE, etc In Adcock s patient, the atelectasis which gave rise to PIE was demonstrated, although its cause was obscure The patient developed PM and SE

Pneumomediastinum and Pneumothorax of the Newborn Although pneumomediastinum has been regarded as a benign condition which will clear up spontaneously, such a happy outcome is by no means the rule, at least, not in the newborn PM alone, or associated with PT, may cause the death of the infant (93), and therefore, its recognition and alleviation are all-important Not all parts of the lung of the newborn child may expand properly Some of the alveoli may remain collapsed owing to the presence of aspirated meconium or amniotic fluid, or to the feeble efforts at respiration The ensuing atelectasis in some regions permits of hyperinflation in others, which, coupled with a poor establishment of pulmonary circulation dependent upon an imperfect closure of the ductus arteriosus perhaps, would bring about the very set of conditions necessary to induce PIE, PM, PT, etc

If the recorded cases of evidence of PIE as revealed by PT or PM are to be taken as an index of the frequency of the condition in the newborn, it is relatively rare If one considers, however, the recent experiences of men who are looking for evidence of PIE then it is much more common than the recorded cases would indicate In a personal communication, Dr Gumbiner said that in the previous six months he has seen four cases of PM, one of which was due to congenital atelectasis Two were in children about a year old with occlusion of the main bronchus by a foreign body, and one had occlusion of the main bronchus, from external pressure of tuberculous lymph nodes Three of these children showed spontaneous PT and two had SE PM is adequately revealed only when the lateral roentgenogram is taken, hence many of these cases may well be missed The final stage of PT, as judged from recorded cases, is rare Bertin, in 1936 found only 22 cases of PT in the newborn recorded in the literature, yet he himself found seven cases in four years by routinely taking roentgenograms of the chests of newborn babies This would indicate that PT as well as PM in the newborn, as in adults, is far more frequent than has been thought

Bertin stated that in only one of the seven cases had delivery been difficult and he thought that perhaps the rough handling of the infant, in an attempt to establish respiration, had some bearing upon the production of PT Secretion entering the larynx immediately after birth might cause a spasm of the epiglottis Both of these factors might operate, or the cause might be found in secretions aspirated before birth

Stransky reported a case in which PM and SE accompanied by PT were found in the newborn In such a case, one may assume that the same factor produced all three conditions, and a rupture of the alveoli due to overinflation provides the logical explanation Ruptured congenital cysts might explain the PT, but not the SE in this child

Slot and Brown stated that SE is rare in the newborn if unaccompanied by trauma Strongin reported a left tension PT and SE in a child that had ex-

perienced a difficult birth After the withdrawal of air, the child's color improved, the mediastinum, which had been shifted to the right, returned to the midline and the child, which had ceased to breathe, began breathing again Strongin assumed that the PT was due to a tear in the lung, but it is more probable that a rupture in alveoli took place, and PIE, with its sequelae, followed McMann and Purcell described SE in a child who was born as a second twin He made gasping sounds as soon as he was born, and became very cyanotic Although the trachea was cleared of mucus, SE appeared, and the child died The left lung was found to be completely atelectatic Here the cause of death was no doubt due to the PIE and its accompaniments, because there is more then enough reserve in one lung to carry on respiration adequately Dogs can carry on with only 15 per cent of the lung present (252)

Silver reviews the literature on PT in the newborn, and adds a case of his own He found atelectasis on the right side and emphysema on the left He removed the secretions blocking the right bronchus through a bronchoscope, but the child died the next day A roentgenogram before death revealed a PT Silver thought that death was due to a ball valve type of obstruction of the bronchus, and that the X-ray pictures supported this view Inasmuch as the obstructing secretions were removed, death was probably not due to them, but to pulmonary circulatory failure caused by the interstitial emphysema on the left side No effort was made to withdraw air from the mediastinum in this child, a procedure which might have saved its life Recent cases of PT in the newborn have been reported by Elkin, Johnson, Pehu and his co-workers, Storts and James, Glaser and Landau, and by Salmon and Forbes Geyman's cases were in infants of four weeks and seven months, although he speaks of them as newborn Attention has been called to PM in the newborn in editorials (73)

Fisher (93) reported a case of PIE and PM in a newborn baby, which died five hours after birth The autopsy was performed one hour after death, and the lungs were fixed by intratracheal injection after their careful removal As the sternum was lifted, air was found in the mediastinum, and also in huge blebs about the pulmonary artery in section The vessels were collapsed by the great accumulation of air in the sheaths, and the air in the mediastinum could not do other than interfere with the action of the heart The left lung had never expanded after birth, consequently the right lung was overinflated Had the air been withdrawn from the mediastinum as Gumbiner does it, with hypodermic needles, this child might have been saved The mere relief of pressure upon the heart and pulmonary vessels, when air is withdrawn from the mediastinum, may tide the infant over the first stages of dyspnoea until the atelectatic lung expands of itself

Cases like this show not only the clinical importance of PIE and PM, but more particularly that there is a malignant PM, causing death This case also shows the value of early autopsy and proper fixation in fatal cases to reveal the cause of death Intrabronchial fixation is advised, but it is important not to overdistend, as this has the effect of pulling the circumvascular alveoli away from the blood-vessels, so enlarging the sheaths and simulating the effect of air invasion

We will now discuss typical instances of aberrant air in infectious diseases, which probably began as cases of PIE

Influenza One of the commonest conditions which has been accompanied by PIE and its extensions is influenza We wish to refer to several papers published during the 1918 influenza epidemic on PIE complicated by SE and sometimes PI There were areas of atelectasis and of compensatory alveolar ectasia in the lungs of patients dying of influenza, and Bullowa ascribed the cause of the SE, as well as of the interstitial air, to the rupture of the parts of the lung showing compensatory emphysema Although aberrant air is a not infrequent complication of the pneumonia following influenza (Torrey and Ghosh had over 1100 such patients), the areas of overinflation caused by atelectasis in pneumococcus pneumonia seem not nearly as prone to leakage into the interstitium This tendency toward rupture of the alveoli in influenza has been attributed to the special necrotizing influence which the influenza virus has on pulmonary tissue (169)

Air was discovered in the vascular sheaths in the lung in some of these cases, and Berkley and Coffen state that the vessel sheaths acted as highways for air from the ruptured alveoli to the hilus of the lung These "air streaks" were demonstrated by X ray Subpleural blebs were also present and Berkley and Coffen stated that air escaped from the ruptured alveoli under the pleura, and, owing to the resistance of the latter, could not get into the pleural cavity Hence it traversed the vascular sheaths to the hilus, ruptured the mediastinum, causing PT, and escaped into the tissues of the jugulum, causing SE They recognized that a common explanation had to be sought for the PT and SE, which coexisted in eleven of their 1,701 influenza cases The primary site of rupture in some instances may well have been in perivascular alveoli as in the experimental animals (188), the air making its way both peripherally to the pleura and centrally to the hilus The entire sequence of events may occur without the presence of pleural blebs Kelman noted SE and subpleural blebs in influenza patients

Clark and Synnott referred to a "gas" in their influenza cases which they interpreted as air from the alveoli of the lungs, occurring in the sheaths of the vessels of the neck, axillae and of the arm as far down as the base of the thumb They noted that the air was not in the muscle sheaths, and that *those vessels in the neck whose sheaths were invaded by air were more compressed and seemed to have less blood in them than vessels elsewhere* Unfortunately the significance of these findings that it was the *vascular sheaths* which were invaded seems to have been overlooked for the most part by later writers, but has been discussed by Macklin (193)

Rohdé and Macklin, working on the blood of patients suffering from influenza in the same epidemic, found that the venous blood was low in oxygen This finding was reported in a monograph on influenza (118) It might be due to several factors (1) the amount of lung involvement was so great that oxygenation was interfered with Against this interpretation are the statements of Kelman and of Guthrie (118) that the dyspnoea and cyanosis in these patients were out of all proportion to the amount of lung involved Moreover, Keith and Corvillos and Bainbridge have averred that only from one twentieth to one tenth

of the lung is needed for respiratory exchange while at rest (2) Some toxic factor acted on the respiratory center to depress respiration Kelman stated that the virus of influenza does depress the respiratory center (3) Some chemical factor in the blood reduced its oxygen combining power Opposed to this are the findings of Rohdé and Macklin that the hemoglobin content was normal as was the O_2 combining capacity, although the rate at which the blood absorbed the oxygen was slow (4) Some mechanical factor, such as an compressing the pulmonary vessels, interfered with the blood flow through the lung (193, 195), or collapse of the lung may have been interfered with because of the inert air in the septa and in the vascular sheaths of the lung There may have been a combination of these factors The marked reduction of oxygen carried in the blood of these influenza patients remains as an observation not opposed to the idea that compression of the vessels by interstitial and mediastinal emphysema, and splinting of the lung by air trapped in its connective tissues, played a rôle in venous stasis and lowered oxygen content

One of us (M T M) recalls vividly the statements of the physicians who collected the samples of blood upon which the O_2 combining capacity was studied "That lad won't be alive tomorrow for you to get another sample from him, he has started to turn black " The deep cyanosis which caused the patient to turn "black," and which almost inevitably presaged death in these cases, we interpret as evidence of airblock The degree to which this obliteration of the lumen can be carried is shown in Fig 2

One cannot read the accounts of Torrey and Gross without being impressed with the likelihood (1) that PIE and PM were present in some of these patients, and (2) that in many cases they were the cause of death

Pneumonia The reported cases of influenza in which PIE has occurred are those in which there has been an associated pneumonia Benjamin reported PT in two children suffering from pneumonia, and interstitial emphysema on the same side in one of these, but thought that the air escaped into the pleural cavity through large spherical bullae This might have been true in his case, although the presence of interstitial emphysema would also account for the PT

Wyatt showed that atelectasis (the essential step in producing local overinflation) was present in 26 or 19 per cent of 135 children with pneumonia This was shown by X-ray photographs It is quite possible that many areas of atelectasis do not show in the X-rays, so that the incidence of atelectasis may have been higher Although Wyatt did not mention PIE or PM as being present in his cases, thus not offering support to our statement that atelectasis is likely to induce these conditions, yet some of his lateral roentgenograms are, in our opinion, strongly suggestive of air in the mediastinum

The opinions of different authors disagree as to the incidence of the sequelae of PIE in pneumonia Cummings states that PT with pneumonia is extremely rare, although he reports a case in a child of nine months with pneumonia Thomas (305), on the other hand, believes it to be more common than the literature would indicate, and reports seven cases of pneumonia with PT as a complication Anderson and Cathcart found it in a four-year-old boy, eight days after

the onset of pneumonia Hurzumache and Pineles reported two children with spontaneous PT after bronchopneumonia, and Watkins reported it in one child It would seem that the frequency with which aberrant air may be found accompanying pneumonia, as indeed in all the other conditions to be mentioned, depends in large part upon the alertness of the physician in suspecting its presence and looking for it

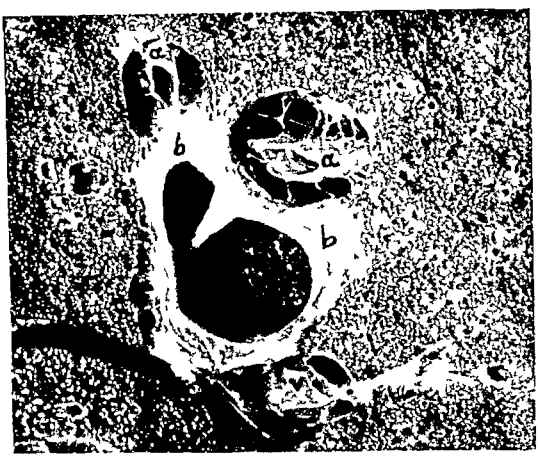

FIG 2 Collapsed pulmonary artery in the lung of a cat in which pulmonary interstitial emphysema had been induced by intratracheal insufflation of air When the pressure was 40 mm Hg PIE had occurred and also PM, because air was escaping from the mediastinum down into the retroperitoneum as evidenced by the marked distention of the abdomen The air also ruptured into the peritoneal cavity so that it escaped from there with a rush when the abdomen was opened later By the time the pressure had reached 100 mm Hg as indicated by the manometer readings the animal was dead Photographs of the lung were taken immediately after death × 5 5

In the upper part of the figure is a cross section of a bronchus just as it is dividing into a smaller branch above and a larger branch to the right *b,b* The pulmonary artery has already divided at a higher level, so that the two branches *a,a*, are accompanying their respective bronchi Note the large amount of air in the sheaths creating a tunnel through which the much compressed artery runs suspended by delicate strands of connective tissue which still project from the outside of the sheath to the vessel wall These cobwebbike strands are particularly well seen in the larger artery projecting toward the right Note the absence of air about the bronchus except where it shares a sheath in common with the vessels Below the bronchus is a vein, *v* partly surrounded by a mass of air

The broncho pneumonia of other infectious diseases may, of course, induce atelectasis, PIE, PM, SE, PT, etc Hence we need not be surprised when these various diseases are reported as having been complicated by air in the interstitial tissue PI may be the only recognized accompaniment, and then it is interpreted in practically all the cases as due to rupture of an adhesion, or of a bulla, or to some tear in the pleural surface, except in those cases in which the patient has come to autopsy, and in which no such bulla, or adhesion or tear could be found, even after the most careful search

Diphtheria Burton records that he found seven cases of diphtheria mentioned in the literature, which were complicated by PM and SE, and added one of his own In this disease, the train of symptoms might be initiated in one of several ways, (1) by local overinflation, following local atelectasis, (2) by increased intra-alveolar pressure occurring during powerful expiratory efforts with a larynx or trachea occluded by membrane or during violent coughing and (3) by dyspnoea following injection of antitoxin (157)

Rolleston (265) reported a child with SE during an attack of diphtheria It might be mentioned here that SE has been designated "surgical" emphysema under the mistaken idea that it appears only following some surgical procedure usually on the neck The vast majority of cases which are called surgical emphysema would appear to be cases in which the sequence of events described in this paper has occurred and that the surgery has had little to do with it except that an anesthetic was necessary for the performance of the operation, and tracheal insufflation of the anesthetic has been practiced, or that the cases needed removal of obstructions in the airway The former cases come under the heading of "general overinflation", the latter under the head of increased intra-alveolar pressure, and will be discussed shortly Rolleston called his case one of "non-surgical" emphysema because it appeared *before* the tracheotomy had been performed The patient had marked dyspnoea which increased in spite of the antitoxin and on the seventh day SE appeared Tracheotomy was performed and gave relief This was no doubt due to the fact that air escaped about the wound, thus relieving pressure in the mediastinum

Rolleston mentioned Sach's case, in which the emphysema extended over the face and chest The child died and it was thought that the trachea had been perforated in the procedure of tracheotomy, but Virchow who performed the autopsy said that the air originated at the "roots of the lung" There was pneumonia of both lower lobes, and there was mediastinal as well as interlobar emphysema This picture is typical, and the observation that the air came from the roots of the lungs is exactly what one would expect The pneumonia, rather than the diphtheritic process, may have been responsible for the whole picture

In the case reported by Senator (265), the emphysema was again attributed to the supposed perforation of the trachea Von Torday's (265) patient had diphtheria complicated by SE, but he recovered The cases of Fabre (265), Pineau (265) and of Sharman and D'Estere (265) all died In the last named case, perforation of the trachea and bronchi was looked for as an explanation of the emphysema, but none was found Dolgopol's patient had not only the SE but also PT Following the suggestion in the former papers of one of us (C C M) that these were due to an initial PIE, Dolgopol looked for and demonstrated air in the interstitial tissues and in the septa of the lung at autopsy The patient of Parseau died 16 days after the onset of diphtheria Instrumental damage to the tracheal mucosa could be ruled out At autopsy, extensive PM was present Two ulcerations on the lateral aspect of the inferior lobe of the left lung were thought to be the cause of the air in the mediastinum, but as we have seen, PM probably arose through an initial PIE Although the PM may not have been the

immediate cause of death in these cases, it undoubtedly was a contributing factor and may have even turned the balance

Acute Obstructive Laryngitis The same remarks made about the classification of diphtheria cases apply to these They may be due to increased intra-alveolar pressure rather than to local overinflation following atelectasis Graebner reported PPC and PM in five children with obstructive laryngitis In four, tracheotomy had been performed from one to two days before the emphysema was noted, and hence Graebner felt that the operation could not be held responsible, but that the onset of acute bronchopneumonia or plugging of bronchi by mucus which had to be aspirated was the cause of the aberrant air In one child the PM occurred before the tracheotomy The anteroposterior view of the chest showed a line parallel with the left border of the heart, which was interpreted as the elevated pericardium with air beneath it

Grier reported a series of 129 patients with inflammation of the larynx, trachea and bronchi whose chests had been x-rayed, fifty-nine showed a widening of the superior mediastinal shadow, which Grier interpreted as enlargement of the paratracheal lymph nodes In a few cases which were followed, the enlargement disappeared spontaneously The same shadows were found in children with bronchopneumonia Grier differentiated them from the appearance produced by enlarged thymus or other mediastinal tumors or from cases of congenitally diseased heart Lateral views of the chest probably would have given the correct diagnosis

Measles As in the case of the other diseases referred to, no attempt has been made to cover the literature on the occurrence of interstitial emphysema of the lung and its sequelae in cases of measles It is to be expected, however, that these conditions will be encountered because measles is accompanied by cough and by pneumonia in some cases Marquezy described two cases in which PM and SE occurred as complications of measles Massey and Oldershaw reported "surgical emphysema" complicating measles The child, aged seven, had a severe cough SE appeared, and the condition was treated by sticking hollow trocar needles into the skin and letting the air out The bronchopneumonia, which had developed before the emphysema appeared, finally cleared and with it the emphysema disappeared also

Smallpox A patient with smallpox accompanied by SE and bilateral PT is reported by Wilkinson At autopsy, edema of the glottis causing forced expiration and increased pressure, and bronchopneumonia causing overinflation were present, either of which would explain the PM which must have preceded the SE A ruptured bulla on the right lung accounted for the bilateral PT in Wilkinson's opinion.

Tuberculosis Of course, the air in the pleural cavities in cases of tuberculosis has been attributed to the rupture of a tuberculous abscess, or cavity, putting a bronchus into communication with the pleural cavity Kirschner (160) stated in reporting an instance in which the actual rupture into the pleura could be found in the wall of the tuberculous cavity, that "The rupture of a tuberculous cavity, however, is rarely seen " This has been assumed to be the explanation of many

cases of PT in patients with tuberculosis A PT may arise, however, in exactly the same way as that described for the experimental animals Atelectatic areas, due to the tuberculous process, might be the cause of compensatory hyperinflation with its train of symptoms Thus, in the patient reported by Blumberg, tuberculosis was advanced There was no history of severe cough immediately preceding the attack, but the patient was found in a confused state, probably due to cerebral air embolism, and with marked SE and a PT Monod reported a case of PM and SE complicating tuberculosis Thompson, also Meade and Stafford, reported cases of tuberculosis accompanied by SE Thompson assumes that the air must have come from a sub-pleural bleb which leaked into the vessel sheaths rather than into the pleural cavity Meade's patient had SE and PT, the former being so extensive as to require incisions into the skin of the neck and chest from which 1200 cc of air were withdrawn He invokes the aid of the sub-pleural bleb to explain the PT, and the escaped air along the vascular sheaths to explain the PM A single cause, namely, ruptured alveoli about the vascular sheaths, explains the PM, SE and PT

An interesting account is that of Dobbie, in which the PIE and PM were undoubtedly the cause of death in a tuberculous patient who did not develop PT spontaneously and in whom it was not induced artificially This man aged 26 had advanced tuberculosis with paroxysmal cough He suddenly developed SE over the whole trunk and down the legs. The cyanosis and dyspnoea became so extreme that the patient died 58 hours after the onset of the acute symptoms Autopsy showed that there was no PT to explain the death The complication of SE in active tuberculosis is rare, Hurrell stating that it had occurred but once in 6266 admissions

Silicosis Silicosis causes a fibrosis of the lungs Such a condition would make for uneven collapse if the lung is undergoing atelectasis, or for uneven expansion if the lung is in a state of hyperinflation to make up for atelectasis in other regions It would not be surprising, therefore, if occasionally PM, SE or spontaneous PT should be found in cases of silicosis In 1940, Moorman stated that eighty-two cases of spontaneous bilateral PT have been encountered in the literature, and added two of his own Nine of these were found in persons with silicosis That more than 10 per cent of the reported cases of spontaneous bilateral PT should have been found in persons who also had silicosis might indicate that the fibrosis of the lung which follows silicosis predisposes to PT, for it is certain that by no means do 10 per cent of the population have silicosis Of course, it may be argued that tuberculosis frequently accompanies silicosis and that tuberculosis is the factor causing the PT, through ruptured tuberculous abscesses, etc The fact still remains, however, that the contraction and fibrosis of parts of the silicotic lung are just the factors necessary to cause hyperinflation in others and thus set in motion the train of events leading to PIE Roubier, in 1937, reported one case of bilateral PT in a mold worker with silicosis Sokoloff, in 1939, found twenty-two cases of spontaneous unilateral PT in a series of 507 coal miners with anthrasilicosis Seven of the cases of PT were found in men who had no accompanying tuberculosis Simultaneous bilateral spontaneous PT was found in a patient with pneumonoconiosis (100)

Foreign Body in the Bronchus From a consideration of the cause of PIE one ight reasonably conclude that aberrant air could be found in patients with a reign body in the bronchus This is not mentioned as a possible complication foreign body in the airway in most of the leading texts on diseases of the chest, it we felt that it must have been observed and recorded A review of the litera-ire showed this to be the case, but revealed that the presence of the air was ually attributed to trauma caused by the attempts at removal of the offending ject, or if such attempts had not been made, the manner in which air entered e tissues was a mystery The experiments here recorded show that there is a rect anatomical pathway for air from alveoli to mediastinum via the vascular eaths, and from the mediastinum to the face and neck and into the pleural vity Atelectasis following the presence of the foreign body produces the first ep in the sequence of events and the rest of the picture unfolds as described Not all cases of foreign body in the bronchus need be followed by PIE Such ases are recorded (164)

Clerf called attention to the fact that metal objects are not often followed by E, although they might be expected to lacerate the tracheal or bronchial walls nd so permit of escape of air into the mediastinum When they do not cause IE, it is doubtless because they do not completely occlude the bronchus PIE nay occur if secretions become blocked behind the metal objects as was the case n McHugh's patient, or if swelling of the mucosa is sufficiently severe so that the irway becomes closed at that point Clerf states that vegetal matter, on the ther hand, is usually accompanied by SE even before bronchoscopy is performed A peanut, piece of popcorn, or coffee bean, etc , is of such shape that it blocks the bronchus and so causes atelectasis, which in turn induces hyperinflation, PIE, etc The irritant oils in peanuts are particularly prone to cause inflammatory reactions in the mucosa which swells and shuts off the flow of air Clerf reported two cases of SE after a foreign body had been aspirated, and cited seven other cases He said "The exact mechanism of production of emphysema in these cases is not known, as none have come to autopsy " Even if they had, the exact mechanism might have been missed, for the story of air invasion is not apt to be revealed if only the usual methods of preserving and examining the material are used Air in the mediastinum may be demonstrated during life by appropriate angle shots, (lateral views), of the mediastinum (10, 249) PM (66, 255) and SE as complications have been reported (311) The PM or PT has been regarded as a result of laceration of the airway (59), sometimes caused by the attempt to remove the foreign body (255), although sometimes the PIE and PM occur before the attempt at removal (152) SE has been produced experimentally by introducing foreign bodies into the bronchus (25) It might be thought at this point that so far there has been no proof from most of these clinical cases to show that the air which was found in the subcutaneous tissues or in the pleural cavity got there through the interstitial route we have outlined This is true, but the cases reported by Fisher and Macklin (94) of foreign body in the bronchus and by Fisher (93) of atelectasis in the newborn, in which intratracheal fixation revealed obliterated vessels and large blebs in the mediastinum, demonstrate that the sequence of events is probably as we have portrayed it Imperatori's case

also affords corroboration This was a child who had aspirated fragments of peanut and developed marked SE The fragments were removed, and the emphysema lessened, but the child died, and autopsy showed that it had developed pneumonia "Pus was also seen along the course of the blood vessels" (of the lung) "and along the course of the trachea" It had followed the course of the air and was in the mediastinum, and around the heart The cause of death was a purulent pericarditis In Rosedale's patient, the PT was on the side opposite to the location of the foreign body

If PIE and its sequelae are to be expected following the impaction of a foreign body, why have they not been more generally recognized? The answer to this is again supplied by the experiments, or rather by the logical deductions therefrom First, if PIE, etc , are to be induced, the foreign body must cause overinflation brought about by atelectasis, and not all foreign bodies are followed by atelectasis, or it must cause increased intra-alveolar pressure, brought about by coughing to expel the object Second, the foreign body may be removed before the stage of leakage of air is reached Third, the presence of pores may prevent atelectasis. Fourth, a child's lung is apt to be free from adhesions, so that collapse may be uniform, whereas in an adult, in which adhesions are more common, a portion of lung which is tending to become atelectatic may be held open in some parts by the presence of adhesions which prevent uniform collapse This happened in Sante's case, which will be referred to under massive collapse The operation of any of these factors or of a combination of them may prevent an overdistention that is severe enough to cause rupture

Pneumothorax. PT has been presented as a secondary effect of PIE, but in some cases it may be the cause, rather than the effect For example, a PT may be present, having been induced artificially, or having arisen through rupture of a subpleural bleb or tuberculous abscess, or through puncture of the lung by a fractured rib, etc If there are adhesions present which bind a part of the lung on the side of the PT to the chest wall, preventing collapse, compensatory hyperinflation may occur in the uncollapsed area Alveolar bases may rupture in hyperinflated areas whatever the cause of the hyperinflation, therefore we may expect PIE in patients who already have a PT as readily as we will in patients in whom the overexpansion follows an atelectasis caused by bronchopneumonia, foreign body, etc The bases may rupture in the hyperinflated areas on the same side as the PT as well as in the contralateral lung

PIE and PM are then likely to follow alveolar base rupture, and further air may enter the pleural cavities by a break-through of the mediastinum This may be on the same side as the original PT, or it may be on the other Since the pressure in the mediastinum had to be high enough to create this rupture, a PT which was perhaps under atmospheric pressure at first may be transformed into a tension PT when the mediastinal pleura gives way

Jessup reported a case in which PT developed from puncture of the lung by fractured ribs After some time the clinical picture changed suddenly (probably from the onset of PIE) Dyspnoea and cyanosis, tension PT and SE developed, and death followed At autopsy, adhesions to the parietal pleura held the upper

lobe from being collapsed by the original PT Thus a PT under atmospheric pressure apparently caused PIE which, in turn, induced PM and tension PT through escape of air from the mediastinum, also SE

PIE may occur during attempts to induce an artificial PT because the needle enters the lung and air is forced into the interstitium of the lung instead of into the pleural cavity This is a different mechanism from the one we have described

The steps by which PT causes PIE are set forth simply as follows Atelectasis may cause compensatory hyperinflation Hyperinflation may cause PIE PT causes atelectasis If the whole lung is not made atelectatic by the PT because of adhesions, PT may be the indirect cause of hyperinflation Therefore, PT may cause PIE

Naturally, the same PT is not at once the cause and the effect, but under one set of conditions PIE can cause PT as the experiments showed (188), or when complete collapse of the lung by a PT is prevented by adhesions, PIE can follow as the result of PT

Some of the patients referred to in this section had benign PM and recovered because the pressure in the mediastinum did not rise to a dangerous level, or when it did, was relieved by escape of air into the tissues of the neck or into the pleural cavity, thus removing the pressure on the pulmonary vessels and heart A goodly number died, however, and death in some instances was attributable not to the initial disease but to the PM Had the condition been recognized, the air could have been withdrawn from the mediastinum, and some of these patients could have been saved

2 Cases in which a Pressure Gradient is Produced by General Overinflation of the Lung (*A*) *Uncomplicated Cases* Relatively few of the cases of PIE, etc , reported in the literature which are caused by general overinflation of the lungs, are those which are not accompanied by some other adverse condition They are complicated either by (1) increased intra-alveolar pressure or (2) reduction in the vascular lumen The first occurs when the patient has a gas blown into the lungs, either in insufflating an anesthesic, or for resuscitation purposes in the newborn, in drowned, or in electrocuted persons The second occurs when the individual has been breathing deeply, as after intense exertion, and the flow of blood to the lungs is reduced for some reason These cases will be discussed shortly

Clinical instances of PIE following general overinflation alone, such as Griffin (113) produced in his dogs, would have to be similar in mode of production, that is, they would result from the sudden lowering of pressure on the outside of the chest, without a corresponding diminution of pressure within the alveoli Such an event could happen when a person ascends from one pressure level to a lower pressure level while still breathing air under the original pressure, or when the change of pressure about the person is so rapid is not to permit of pressure adjustments in the alveoli in the ordinary course of breathing Thus a person would experience general overinflation of the lung unaccompanied by increased pressure or reduction in blood vessel caliber if he were in a theoretical airplane

which rose so rapidly that decompression of the chest occurred before the pressure in the lungs could be altered by breathing, or if he were suddenly shot up as a projectile from a mine, or from a caisson With more gradual decompression he could also experience this type of general overinflation if he were fitted with a tight mask and were made to breathe into a container in which the pressure was maintained at that level at which the ascent had been started Finally, uncomplicated general overinflation occurs in bomb-blast lungs, for in blast the decompression wave is very intense and of such short duration that there is no time to adjust pressures in the alveoli by breathing in the rarefied atmosphere These cases will be discussed later, because there is a probability that PIE may also occur during the compression phase of bomb blast as well, since the other pulmonary lesions, such as hemorrhages, are produced also in the compression phase (337)

(B) Combined with Increased Intra-alveolar Pressure Most of the cases of general overinflation of the lungs which have been accompanied by PIE, PM, PT, SE, etc , are those in which the overinflation has been coupled with increased intra-alveolar pressure Such cases would correspond to the experimental animals in which air was blown into the lungs through the trachea (188)

Resuscitation of the Newborn, or of Persons in whom Some Type of Pulmotor is Used Although the majority of cases of PIE in the newborn are probably the result of compensatory local overinflation accompanying areas of non-inflation, (congenital atelectasis) some cases are the result of forcible blowing of air into the lungs of the newborn infant in an effort to start respiration Rothman mentions the use of forcible artificial respiration and of the Drinker respirator as causes of spontaneous PT in the newborn Smith and Chisholm found that the chest of the newborn infant, in its efforts to expand, exerted a pressure equal to 40 cm of water (31 mm Hg) They argue, therefore, that pressures as high as this may be used in resuscitating devices This conclusion does not necessarily follow It is possible that this pressure may not be excessive but the force required to expand the atelectatic portions of the lung may be sufficient to rupture those areas showing compensatory hyperinflation From our experiments we would say that such pressures were likely to prove dangerous

Insufflation Anesthesia Because of the not infrequent appearance of SE following operations, it has been called "surgical emphysema" It appears to be much more common following those operations in which the anesthetic has been administered intratracheally under pressure than in those in which it has been given by the inhalation method, also to be common in operations for relief of obstruction in the airway Sometimes the condition arises because atelectasis has occurred, either through aspiration of material, such as blood or pus, during the operation, or through loss of tonus of respiratory muscles during a prolonged surgical procedure Some of the cases result from too high a pressure of gas entering the lungs, however, and it is dangerous to use such insufflation methods without carefully watching the pressures used Lilienthal's case was one in which PM followed insufflation anesthesia at a pressure of 60 mm Hg according to Joannides and Tsoulos.

Interstitial air has been found following thyroidectomy, tonsillectomy and abdominal operations, especially on the kidney No attempt has been made to collect all these cases, for in the majority of them the same factors are operative, namely, general overinflation of the lungs by too great a pressure of gas being blown in or hyperexpansion of some areas, when others are atelectatic, both conditions creating a pressure gradient from alveoli to vessel sheath

Some modern treatises on anesthetics do not mention this condition as a possible complication of administering anesthetics under pressure Two such modern works were available to us (133, 264), and in one this was not mentioned, in the other (133), it was stated (although not in the section on complications following anesthetics) that there is not much danger of the pressure being too high if "reasonable" care is exercised, inasmuch as it has been shown that dog's lungs would not rupture, even with the chest opened, until the pressure under which the gas was blown in exceeded 120 mm Hg McKesson, whose experiments served as the authority for Hewer's statement, said that the lung of the dog would not rupture under the application of a pressure of 120 mm Hg McKesson probably meant that the *pleura* would not rupture, for PIE can be produced in dogs at pressures of 80 mm Hg (256) The alveoli rupture at a pressure far less than that necessary to tear the pleura PIE can be produced in cats and rabbits and also in man at much lower pressures From our experience, we would say that this is a most dangerous pressure to use Most articles which give the pressure under which the anesthetic is blown in state that it is controlled at 25 mm Hg Cotton and Boothby recommend that it be no higher than 10 mm Hg In view of (1) the findings here reviewed, (2) the ease with which PIE can be produced by blowing air in under pressure, and (3) the real threat to the life of the patient when PIE and PM occur, the whole matter of the maximum pressure compatible with safety in the administration of anesthetics should be carefully reinvestigated, and the pressures rigorously controlled It should also be remembered that a pressure which is safe perhaps at the beginning of the anesthesia, when the secretions from the bronchi have not yet accumulated, or safe for a person who is not suffering from an infection of the airway, may be dangerous later on in the course of the operation, when the airway may be blocked with secretion, aspirated blood, etc , or when the alveolar bases have been weakened by disease Pressures which are safe when the lung is supported by the unopened thorax may prove much too high if the thorax is opened It is doubtless the case that some of the postoperative deaths which were in reality caused by the PIE and PM arising during the course of administering the anesthetic, have been regarded as attributable to the surgical procedures rather than to the compression of the pulmonary vessels by escaped air Also, this complication probably arises in some patients, but is mild and does not cause death In such cases it almost always goes undiagnosed

When patients, who have just had an operation, show an undue amount of dyspnoea and cyanosis, the presence of PIE and PM should be suspected, and steps taken either to verify or to rule out the presence of air in the mediastinum

If air is present, the administration of oxygen is not likely to be of much assistance, as the vessels are too compressed to permit of much flow through the capillaries, and hence of absorption of oxygen Withdrawal of air from the mediastinum will be of much greater benefit than the administration of oxygen.

PIE and PM Following Operations Barrie recorded postoperative PIE and PM after *thyroidectomy* in two cases, and after operation on the glottis in a third.

In the first case, the intratracheal anesthetic produced coughing and cyanosis, whereupon the anesthetic was administered by the open method Cyanosis deepened, the patient's condition became steadily worse, and death occurred nine hours later At autopsy, SE, PM and PT were found, also air about the pericardium. The bronchi and trachea were filled with tenacious mucus When the lungs were filled with air while they were under water, no leakage was found except at the pulmonary ligament This was where the air was found escaping in the cats whose lungs had undergone local overinflation (188), also in calf's lungs (196)

The history of the second patient was much the same, with bilateral PT and with no detectable perforation of the trachea or pleura, either visceral or parietal Again there were quantities of mucus in the bronchi The third case developed bilateral PT and SE after a tracheotomy to relieve edema of the glottis. Interstitial air after a *radical dissection of the neck* occurred in Ackerman's patient

Keis collected seven cases, all fatal, of mediastinal emphysema following thyroidectomy Four of these had bilateral PT as well In two of the patients, PM was observed during the operation Waltman and Leach report another case of PIE and its sequelae following thyroidectomy Keis was able to produce PT in a corpse by inflating the mediastinum This is what would be expected.

Hernandez' patient died as a result of ballooning of the mediastinum and the subcutaneous tissues after *thoracoscopy* We do not know the mechanism of PM production in this case, since the article was not available Ehrlich (78) found retroperitoneal air in his patient, upon whom a *kidney operation* was performed, when he first opened the abdomen, showing that it was not the operation, but the anesthetic under pressure which first caused the air to escape into the interstitial tissues When the operation is on the neck region, there is always the tendency to interpret the interstitial air as being caused by a nick in the dome of the pleura, or laceration of the trachea Ehrlich though that there must have been an abrasion of the pharynx or larynx in his patient, produced by the insertion of the tube for giving the intratracheal anesthetic, which caused the air to gather behind the peritoneum, since the anesthesia pressure was always controlled at 25 mm Hg. SE developed in this patient about the face and neck later Mathé and Faulkner's patient was also one in whom the operation was on the kidney Because the prone position is the one usually assumed by the patient for operations on the kidney, anesthesia is induced intratracheally, this being more satisfactory from the standpoint of the anesthetist than by the inhalation method Therefore, PIE and PM would be expected more often in operations upon the kidney than in those for removal of the appendix, for example

Two recent cases have been reported in which the true course of events was recognized Eisen's patient, a child of four years of age, had an impacted coin in the esophagus Ether was given by insufflation into the nasopharynx, whereupon air appeared in the subcutaneous tissues of the neck, in the thoracic cavity and in the retroperitoneal spaces He explained these findings upon the basis of the results of the experiments outlined earlier in this paper Another patient developed PT and SE following an operation in which insufflation anesthesia was used (129)

Tracheotomy is not infrequently followed by PIE Michels reported six cases in whom PIE, PM and PT developed In one of these patients, atelectasis with compensatory emphysema followed the aspiration of a screw After the screw was removed, the lung reinflated, but the lower right lobe again became atelectatic, no doubt due to a bronchopneumonia Tracheotomy was performed, and the next day SE and PT were present The child recovered In this case, the aberrant air might have resulted from the first or second attacks of atelectasis in the lung, or from the administration of the anesthetic for the tracheotomy

The second patient had a congenital stenosis of the larynx, with cough and dyspnoea, for which the tracheotomy provided little relief Bilateral PT developed and the child died The bronchi were filled with exudate, both upper lobes were atelectatic, and both lower lobes showed hyperinflation Here again, the operation was probably not responsible, the PT being due to an initial PIE caused either by local overinflation of alveoli or by increased pressure in the lung generated by coughing against a stenosed larynx, or by a combination of the two

The third child had had measles six days before It became cyanosed, with labored breathing The tracheotomy afforded relief for but a short time, SE appeared and the child died five hours later Marked PM, bilateral PT and atelectatic areas in both lungs, accounted for by necrotic membranes filling both trachea and bronchi, were found at autopsy The tracheotomy was probably not responsible for the PM in this child The atelectatic areas producing compensatory hyperinflation, together with the increased intra-alveolar pressure induced by expiring through the narrowed airway are sufficient explanation for the PM and PT which occurred Clearing of the bronchi by suction and removal of air from the mediastinum would perhaps have saved this child

The other three cases had similar histories Two of them recovered and one died At autopsy, no air was found about the larynx or trachea, as would be expected had air been sucked in through the tracheotomy wound, but massive blebs were found over the heart and along the pulmonary vessels These cases of Michels should be regarded, not as examples of PIE complicating the operation of tracheotomy, but as instances either of local overinflation dependent upon local atelectasis resulting from exudates in the airway or from bronchopneumonia, or of increased intra-alveolar pressure arising through strong expiratory efforts against the resistance of an obstructed airway They have been included in this section for the sake of the reader who may be trying to interpret PIE, PM, etc in cases of his own after tracheotomy

Forbes and Salmon report four patients with PM following tracheotomy The first child developed PM and bilateral PT five hours after the insertion of the tube for laryngeal diphtheria The second child inhaled a grape fruit seed, and atelectasis of the left lung with compensatory overinflation of the right lung ensued Tracheotomy was performed and bilateral tension PT followed The third child inhaled a chicken bone, PM developed as revealed by roentgenogram, and suction of air from the mediastinum was attempted but without success, apparently because the needle was not moved around to enter all the air pockets in the mediastinum The child died At autopsy, no air was found in the pleural cavities but much in the mediastinum In the fourth patient who developed bilateral PT, the air was removed from the pleural cavities and the child recovered In this group of four, there was one death definitely due to malignant pneumomediastinum The other two deaths were directly due no doubt to the collapse of both lungs, but the PT was in turn the direct result of PM It is, therefore, not as harmless as some have surmised

Sometimes the evidences of PIE occur *before* the tracheotomy is performed The patient of Neffson and Bullowa had influenza, developed bilateral PT before tracheotomy, and SE appeared after the operation Despite the removal of air from the pleural cavities which caused a temporary improvement, the child died Cook's patient also had extensive SE before tracheotomy At the operation, the trachea was found to be flattened by the extreme pressure of air in the mediastinum and tissues of the neck Despite the relief afforded by the operation, the child died, probably because the pulmonary vessels both in the lung and at the hilus were as flattened by air pressure as was the trachea

Most authors look for two explanations for interstitial air in tracheotomy cases· (1) they seek for an explanation of the PM, PT and SE which occurs *before* tracheotomy and another for the same conditions when they *follow* tracheotomy, without realizing that the essential factor causing PM and PT may be and frequently is the same in both, and is the initial condition which called for the operation Tracheotomy is merely incidental, the cause of the rupture being increased intra-alveolar pressure resulting from the stenosed airway The explanation advanced for the presence of interstitial air before the operation may be the rupture of the sub-pleural bulla which is assumed to be present, or the rupture of alveoli as given earlier in this paper Neffson (231) calls the latter the "intrinsic" route and says that it is the mode of production of PM which occurs before tracheotomy. The "extrinsic" route (sucking air in around the tracheotomy wound) is thought by Neffson to be taken by air in those cases which have been operated upon Work, also Goldberg and his associates, regard the extrinsic route as the one taken by air in their patients when they developed PM and PT after tracheotomy was done The latter authors feel that they have proved their point by the experiment in which they "blew air" into the mediastinum along the cervical fascial planes and produced PT It should be noted in this connection, that in the patient with a wound in the neck, air is not blown in, but is sucked in, until the pressure in the mediastinum, normally about 4 mm H_2O less than atmospheric (144), reaches the atmospheric level Once it reaches that

point, it cannot go higher by being sucked in through the wound A pressure in the mediastinum, no higher than atmospheric, might not be sufficient to cause its rupture into the pleural cavities The work of Ballon and Francis on rabbits suggests that on these animals pressures higher than atmospheric are necessary to rupture the mediastinum to cause PT When air is *blown* in, as was done in Goldberg's experiments, it is of necessity blown in at pressures *above* atmospheric, and it is not to be wondered at that the mediastinum ruptured giving PT This finding is quite in agreement with our experiments here recorded When the mediastinal pressure is raised sufficiently above normal, whether the pressure be caused by air *coming into it by way of the pulmonary vascular sheaths, or* by air blown into it from above, the mediastinum may rupture to produce PT Goldberg's experiments merely added confirmation to this known fact, but did not prove that the air in the mediastinum in his patients had come there via the tracheotomy wound It cannot possibly get there by such a route when the tracheotomy has not yet been performed

Certain of Neffson's observations are not in line with his conclusions drawn from them, that the extrinsic route is always taken by air once the operation of tracheotomy is accomplished He says that with the increased use of the tracheotomy tube there has been a lowered incidence of PT, the incidence dropping from 25 per cent in the unoperated cases to 8 per cent in the patients with the operation If tracheotomy, *per se*, was the cause of PM and PT, the incidence of the latter should rise, *pari passu*, with that of the operation If on the other hand, the obstruction of the airway producing increased intra-alveolar tension is the primary cause of PM and PT, the increased use of tracheotomy (therefore the earlier relief of obstruction) should lower the incidence of PM and PT The incidence of the latter is lowered while the incidence of the operation has risen The inference is clear that the operation cannot be the cause of PM and PT in the majority of cases

In further, although unintentional, support of this interpretation that it is the increased intra-alveolar pressure caused by the obstruction rather than the operation of tracheotomy that is responsible for PM and PT etc in most of these cases, is Neffson's statement that intubation, (which of course relieves the obstruction and lowers the intra-alveolar pressure) before tracheotomy also reduces the incidence of PM and PT These complications followed in 18 per cent of the 33 cases without intubation, and in but 12 per cent of the 93 cases with intubation

Neffson states that PT occurs in 60 per cent of cases after tracheotomy and feels that there must be a causal relationship In his own series of 126 cases, it occurred in but 17 or 13 5 per cent (230) This may be due to earlier operative procedures in his series, thus inhibiting the appearance of PIE The incidence of PT and PM would be much more nearly 100 per cent in cases needing tracheotomy, were the operation not performed We point out here that the cases with severe obstruction to the airway, hence the cases on whom tracheotomy is done, are the very ones in whom PIE, PM, PT are likely to occur The reason for their appearance after the operation rather than before is sometimes to be found in the delay which occurs after the initial rupture and the recognition of the symp-

toms of interstitial air The patient is having marked difficulty in breathing, rupture of alveoli takes place, the compression of the pulmonary vessels by air increases the respiratory distress, the physician decides to relieve the respiratory distress by insertion of a tracheotomy tube, and does so, but in the meantime air has been making its way toward the hilus of the lung and into the mediastinum Depending upon the time at which the operation was done and whether the operation provided complete relief, PM and PT may or may not occur If the operation is *performed quite early* and if it affords *complete relief*, PIE, etc, may not have had time to occur before the operation and the factors causing it to occur are now done away with If it has had time to occur, the leak will probably stop with the institution of an open airway, but the air already in the interstitium will be moved along towards the hilus Depending on its amount, it may or may not be sufficient to cause symptoms If the operation is *done early*, but *does not afford complete relief* because the tube becomes blocked with secretions, or the swelling of the trachea and bronchi below the level of the tube continues to occlude the airway, PIE may not occur until after the tracheotomy has been performed, but it is not because air is sucked in through the wound that PM develops, but because the operation does not accomplish its purpose and the excess intra-alveolar pressure still continues and causes alveoli to rupture and air to travel along vascular sheaths to the mediastinum If the operation is *done late*, although it affords *complete relief*, PIE is likely to have occurred In such a case, the aberrant air may be recognized by its symptoms before the operation is done, or, if the amount of escaped air was small, it may not reach the mediastinum and elicit symptoms until after the operation has been performed In the latter case, the operation will be blamed for the PM If the unfortunate combination of *late operation* and *incomplete relief* occurs, then air which may have escaped before the operation, continues to escape through the leaking alveolar bases after operation, and PM, PT, SE, etc may all develop and the child may die

We have gone into this discussion at some length, for it is difficult for those who have not visualized thoroughly the mechanism of alveolar rupture and its causes, to see that this indirect, obscure route may be taken, rather than the supposed route through the tracheotomy wound We do not say that air cannot be so sucked in, and in some cases it definitely enters by that route, as shown by the sucking noise on inspiration, but point out that the same mechanism which caused interstitial air when there was no operation on the neck, may have started an identical train of events before the operation, although not becoming obvious until some time later Or it may start these events after the operation, if the obstruction is not completely relieved. Although the extrinsic route may be followed in cases of tracheotomy and dissections of the neck, (and in such cases there will be PM, but no evidences of PIE) the air may equally well follow the intrinsic route Neffson's observation that tracheotomy lowers the incidence of PM would indicate that the intrinsic route is probably the commoner of the two

Tonsillectomy We do not know who first explained the PIE, PM, etc , following tonsillectomy as due to the following causes, but these reasons for the em-

physema have been repeated from author to author with apparent amazing lack of critical thinking It has been suggested that the SE of the neck and face in these cases may be due to (1) air entering the tonsillar bed after the operation, (2) air or anesthetic being forced into the parotid duct from the tip of the anesthetic hook, (3) ruptured vesicle under the pleura, followed by dissection of air under the pleura around to the hilus, thence to the mediastinum, etc Parish recorded the onset of SE in his patient ten minutes after the operation He does not mention the mode of administering the anesthetic The case may have been one of local overinflation following atelectasis through aspirated material, but the rapid onset of the emphysema would suggest the anesthetic as the cause

In Rosenheim's patient the SE was noted eighteen hours after the operation, so that atelectasis and overinflation may have been operative here Rubenstein's patient developed emphysema within thirty minutes of the operation He coughed violently and continuously after the operation, so that the overinflation may have been general, caused by the violent expiratory efforts of coughing This author put forward the three explanations advanced above as to the origin of the aberrant air

In the first case of Richards, the emphysema did not appear until the morning following the tonsillectomy, and Richards invoked the subpleural vesicle and subpleural route of air to the hilus as the explanation in this case The second patient had a unilateral emphysema, and Richards felt that here the air was sucked in through the tonsillar fossa Von Hofe's patients also exhibited unilateral emphysema He stated that the anesthetic was administered by the open cone method in the first stage, but after that by the pump method, with the hook-shaped metal tip of the anesthetic tube suspended from the right side of the mouth If the anesthetic was blown in under pressure, and if secretions of the trachea occluded the lumen, the anesthetic may have been blown past the plug, which prevented escape of air Too high pressure could then certainly have produced the symptoms Del Chicca felt that the ether tip in the mouth might have been forced against the parotid duct, thus blowing gas back into the gland Keen criticized the idea that air could be sucked in through the empty tonsil bed, or forced into the parotid duct, and felt that overdistended alveoli ruptured He made the mistake of thinking that it was along the bronchi rather than along the blood vessels that air travelled to the mediastinum

Dickson, MacCready, and Judge have all reported SE following tonsillectomy MacCready explained the SE in his two patients as arising through increased intrathoracic pressure in the patient in whom there were tremendous spasms of coughing, and in the other through obstruction, since the patient was attempting to breathe with the teeth tightly clenched

All of these cases were probably examples of PIE, PM, SE, etc , produced by either (1) local or general overinflation arising through compensatory mechanisms, set into operation by atelectatic areas, or by blocked airway, or by anesthesia administration, or (2) raised intra alveolar pressure accompanying coughing

B Involving Factor B Cases in which a Pressure Gradient is Produced by Reduction of Caliber of Blood Vessels

It was stated that the essential factor in PIE is a pressure gradient between air in the alveolus and the connective tissue underneath, leading to a rupture of the confining base of the alveolus If air is to flow toward the mediastinum, the leak must continue, and the air must be pushed along by respiratory movements The first method of producing this gradient (Factor A), namely, by enlarging the bases of the alveoli about the blood vessels through hyperinflation, has already been discussed We shall now consider the second method of producing this gradient (Factor B), namely, by reducing the caliber of the pulmonary blood vessels through decrease in blood flow This could be accomplished (1) by a lessened return of the venous blood to the right heart, (2) by a failing heart which could not send out the normal amount of blood to the lungs, (3) by stenosis or insufficiency of the pulmonary artery valves, or (4) by an obstruction in the pulmonary arteries as in the case of pulmonary embolism In most instances, in which there is a lessened return of blood to the right heart, there is an associated factor of increased intrapulmonary pressure, so that two factors are cooperating to produce rupture of alveolar bases When PIE occurs in relation to failing right heart, the reduction in vessel caliber is usually associated with hyperinflation Thus Factor B operates frequently in conjunction with Factor A or with increased intrapulmonary pressure, or with both

1 Uncomplicated Cases. *Pulmonary Embolism* We have not seen the presence of PIE, PM or PT recorded as accompanying disease of the pulmonary valves, although theoretically they might be expected One patient developed PT following pulmonary embolism (60), and this would seem to be a case in which Factor B was the principal explanation

2. Combined with Increased Intrapulmonary Pressure How can lessened venous return to the right heart be obtained in these patients who develop PIE, etc ? It is accomplished by making a forced expiration when the glottis is partly or completely closed, or by expiration when the bronchi are stenosed or blocked by tenacious mucus

As in all expiration, the flow of blood towards the thorax from the abdominal and cervical veins is inhibited to a certain extent, so that the right auricle, and consequently the right ventricle and the pulmonary circulation, receive less blood. This means that the caliber of the pulmonary arteries and veins during the expiratory phase is reduced In addition, the pressure in the alveoli rises because the expiratory efforts are made against a closed outlet

Blood is dammed back from the thorax, causing congestion of the neck and face, particularly in persons who are coughing or straining violently As the heart continues to beat throughout this period, although little blood is being brought to it, the pulmonary vessels become still further reduced in caliber, and the sheath is put under increasing strain, between an ever-narrowing inner circle and a stationary outer circle This causes a reduction of pressure in it, while against it lie the alveoli under pressure much above atmospheric The alveoli rupture, and as there is a pressure gradient, air flows along the vascular sheaths

Here again conditions are such as not to favor rupture into the bronchial sheath Although the alveoli abutting upon the bronchi are under increased pressure, so is the bronchus which is sharing in the pressure generated by the contracting chest wall on air which cannot escape through the closed glottis Therefore the peribronchial sheaths are not subjected to a pressure gradient as are the vascular sheaths Although we have not found that PIE without its accompaniments has been described in patients making strong expiratory efforts with a closed glottis, we found cases in which the PM and PT were probably sequels of initial PIE

At this point we would like to make one thing very clear We have said that entrance of air into the vascular sheaths compresses the pulmonary vessels, we have also said that the decrease in size of the pulmonary vessels may be a factor in causing air to enter the vascular sheaths It may be objected that we cannot have the same factor as both cause and effect Diminution in size of vessels cannot be caused by and *at the same time* cause entrance of air into the sheath This is quite true, of course But it is equally true that *at different times and under different circumstances* entrance of air into the sheath may compress the vessels or the entrance may be caused by a diminution in the size of the vessels coupled with increased alveolar pressure If the pressure gradient is caused by hyperinflation of alveoli (Factor A), air enters the vascular sheath, and the vessel is compressed secondarily (Figures 2 and 3) If the pressure gradient is caused by a combination of (1) diminished blood flow through the lungs (Factor B) and (2) increased alveolar pressure through forced expiration with glottis closed, the vessel size is lessened first, and air enters secondarily When the glottis is opened and normal inspiration is again in effect, the air in the sheath serves to keep the vessels compressed

One might inquire why it is that PIE does not occur in all cases of violent cough, childbirth, asthma or strenuous exercise, etc It probably occurs much more frequently than we realize, although it does not grow to clinically recognizable proportions unless the pneumatization of the pulmonic connective tissue is marked Thus, although the woman is straining during parturition, the strain is not constant, and when birth is over the factor inducing a pressure gradient is ended, and with it ends the leak, if one has occurred Hence only in extremely prolonged labor or unduly vigorous expulsive efforts would the air leakage be sufficient to get into or even beyond the mediastinum and produce recognizable symptoms There may be also a constitutional factor which explains the occurrence of PIE in some cases and not in others Not until we know a great deal more about the incidence of PIE will we be able to say whether it is a rare accompaniment of these cases

Parturition In childbirth the stage is set for the production of PIE and its successors Forced expiration with the glottis closed increases the intrapulmonary pressure so that the alveoli may rupture Leading texts on obstetrics which were consulted did not mention this aberrant air as a complication of parturition, but a search of the literature showed that such cases have been reported, at least as far back as 1876 (243) Gordon had collected 130 cases in 1927, and Nussbaum in 1937 had collected another 12 and reported an additional case He stated that the etiology is unknown

Although the number of recorded cases was only 143 in 1937, that by no means represents the incidence of the condition Phillips (254) had not had a single case in 3000 deliveries but in the next 3650 deliveries it occurred five times, an incidence of 1 in 1110 cases

The reason for the apparent rarity of PM alone or accompanied by SE during parturition may lie (1) in the fact that PM is less common in the female than in

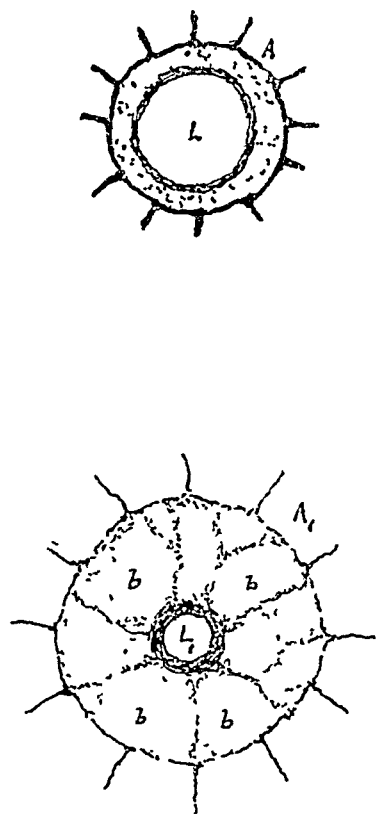

FIG 3 In figure 1 are shown the initial steps in the break-through of air into the vascular sheaths This figure shows the end result of break-through of air from overdistended alveoli (Factor A) When air invades the sheath in sufficient quantity it compresses the vessel, so that the lumen is much smaller The upper part of the figure shows a normal pulmonary vessel with its surrounding ring of alveoli, *A* *L* is the lumen The lower part of the figure shows the lumen compressed, L_1, the distended alveoli, A_1 and the numerous bubbles of air—*b*,*b*, which have compressed the vessel This diminution of size in vessel caliber is here a *secondary effect* of the invasion of air, and not the cause of the air invasion which happens when Factor B is operative The result, however, is comparable to that caused by a simultaneous operation of Factors A and B, as in Figure 1 E For discussion see text

the male, or (2) in the assumption that it is found less often than it occurs because the obstetricians have not been trained to look for it, and are focussing most of their attention elsewhere in their patient's anatomy Only when the lesion is extreme enough to cause distress on the part of the patient is it likely to be noted by the doctor If the obstetrician is taught that PIE, PM, SE or even PT with grave respiratory and circulatory distress might occur from too vigorous expulsive efforts on the part of the patient, not only will he be more liable to recognize

these conditions when they occur, but he may be able to warn against too much bearing down, and so forestall them

Phillips (254) feels that the explanation lies in a congenital *weakness of the tracheal or bronchial walls* which he supposes may break down under the straining, allowing air to leak into the mediastinum Other explanations which have been advanced are (1) rupture of the traditional emphysematous bleb (282) to explain PT, or even a ruptured lacrimal bone during labor (253) to explain SE over the face, although how a lacrimal bone could be ruptured during labor is not clear

The prognosis in these cases is said to be invariably good (254), although two deaths have been reported from this cause in parturient women (158) The reason for the good prognosis is obvious The increased intra-alveolar pressure is a temporary one, with the cessation of the expulsive efforts in the second stage of labor, the excess pressure and the leak come to an end It is only when the second stage is very prolonged, giving opportunity for accumulation of enough air to cause symptoms, that the condition may become serious Lateral roentgenograms of the chest should be taken of women who show signs of marked respiratory distress following childbirth, to determine whether there is air in the mediastinum or pleural cavity SE in such women seems to be the most frequently recorded complication (37, 56, 67, 90, 111, 137, 158, 202, 211, 216, 233, 242, 289, 296)

Violent Straining Not only in women in childbirth, but in other persons who are making strong expiratory efforts with the glottis partly or completely closed, are the effects of PIE to be sought Young reported two cases in the same family in which PT resulted after violent straining at stool The mechanism is undoubtedly the same as that which takes place in parturition One may postulate a subpleural bleb in these cases, but ruptured alveoli and PIE are much more likely to be the explanation The patient of Emerson and Beeler died as a result of straining in the act of defecation, although the primary PT had been caused by the forcible expirations of asthma Kahn's (149) patient developed air in the pleural cavity from lifting an 80 pound sack of beans He had been an asthmatic for years Walinder's patient developed bilateral PT after lifting a heavy carcass weighing 90 pounds In another patient (212) in whom SE appeared, the course of events is not clear A male aged 62 had pain in the abdomen with vomiting The next day emphysema of the neck was noted When he was straining to evacuate an enema, the swelling in the neck suddenly became much worse The abdomen had become very swollen following the cramplike pain At operation, large amounts of air escaped from the peritoneal cavity and a perforated duodenal ulcer was found The patient died, and no autopsy was allowed For six weeks before death this man had suffered from a severe cold with purulent sputum The initial PM may have been produced by atelectasis of part of the lung, or by coughing to expel the sputum, or by escape of air from the ulcer, the sudden increase in the amount of air was due to straining to get rid of the enema These authors (212) review the literature on subcutaneous emphysema following perforation of the gastro intestinal tract which is a rare, but recognized, complication of such perforation They point out that the route

which the air takes is obscure in such cases. In Groth's patient, subcutaneous air vesicles, arising from excessive straining to clear the throat, became so large in the neck that they occluded the cavity of the pharynx, and had to be incised to permit of respiration.

Whooping Cough, or any Violent Cough The forced expiratory efforts of whooping cough may obstruct the return of the venous flow as well as raise the intrapulmonary pressure If the pressure gradient is sufficient, alveolar base rupture may occur SE was found in such a series but once in 1200 cases (333), but the frequency of PIE was probably much greater, most of the cases not going on to the manifestation of SE A severe coughing attack, no matter what its cause, may produce PIE and its sequelae, as in Caldwell's also in Watkin's patients

Asthma In 1938, the Rosenbergs collected eighteen cases, including their own, of SE (and, of course, PM also) following asthmatic attacks Two others, not mentioned by them, have been recorded. Faulkner and Wagner's case proved fatal, and the patient of Elliott would probably have died had not incisions been made over the skin of the chest to allow air to escape. Kirsner explained the presence of SE as follows "The rupture of an emphysematous bleb or of a cavity apparently permits air to extend through the interstitial tissue of the lung into the loose cellular tissue of the mediastinum, and from there into the subcutaneous tissues of the neck and face, etc." As has been shown (188), SE occurs in cases in which there are no emphysematous blebs, and is due to rupture of alveoli about the pulmonary vessel sheaths Sheldon described SE in an asthmatic patient, and explained it by saying that there was a congenital weakness of the pleura, so that subpleural alveoli ruptured, and air dissected its way to the mediastinum via the bronchi and blood vessels We affirm that alveoli situated anywhere in the lung, not necessarily under the pleura, may rupture.

Other authors have reported asthma complicated by SE (41, 61, 69, 150, 182, 240, 280, 302, 310, 318, 323) The PM which must precede the SE was looked for and found in Dietrich's patient. Skinner tried to interpret the SE in his patient as having been caused by air which had ruptured from the mediastinum directly into the tissues of the chest, stating that air could not possibly have made its way from the mediastinum through the jugulum into the neck as the anatomical arrangement of fascia at the jugulum makes this impossible, according to him He felt that air could not dissect its way along the vessel sheaths, although this is the route which we have found it to take

PT is not mentioned in medical texts as a complication of asthma, but we felt that PT was to be expected sometimes in asthmatics, because of the method of its production Therefore we looked for such reports, and found them We mention only a few of these Blanco and Pastorino reported cases of PT and SE in asthmatic patients The patient of Castex (44) had unilateral PT and that of de Carvalho had had bilateral PT Elliott's patient is of interest because the air in the pleural cavity was under no tension, while that in the subcutaneous tissues of the chest was under such pressure as to threaten the life of the skin above it.

Removal of air from the chest gave no relief, while incisions into the skin of the chest gave spectacular relief This difference in pressures in the two locations might lead one to suspect that two mechanisms were at work producing air This is not a necessary assumption, because air escaping into the pleural cavity could expand by further compressing the lung, thus preventing a rising pressure Air in the subcutaneous tissues could only expand to the limit of elasticity of these tissues, and any further increments of air would cause an increasing tension

A very recent case of asthma (91) has been reported in which spontaneous PT, massive collapse and SE all appeared as complications in a child of four

Craige reported seven fatal cases of asthma He spoke of all of them as having voluminous lungs, bulging out over the mediastinum Five patients had a terminal dyspnoea and four a marked cyanosis These lungs were not only voluminous owing to loss of elastic tissue, but they actually expanded after removal of the sternum, showing that the air in them was under pressure Was this air trapped in alveoli and small bronchioles behind larger bronchioles and bronchi whose lumens were occluded by exudate or by muscle contraction? Or was it trapped in connective tissue septa and about blood vessels from which it could not escape? Many of the reports of such patients stated that they had responded to epinephrine before, but in the terminal attack it did no good This fact may indicate that dilatation of air passages was no longer efficacious for liberation of air because the air was no longer trapped in the airway, but in the interstitial tissues from which it could not escape

Not all lungs of persons dying in an asthmatic attack balloon out over the mediastinum, in fact, in some patients they collapse when the chest is opened (162)

In some asthmatic patients, however, the lungs do bulge out of the chest when it is opened (35, 55, 136, 260, 303) PIE may not explain this increased lung volume If PIE is present, fixation of the lung by intratracheal injection as speedily as possible after death will be more likely to reveal it than will the ordinary methods of fixation Not all asthmatics will have PIE or its sequels, but the increased intra-alveolar pressure which is present in asthma is often conducive to the formation of PIE

One might inquire why PIE and its accompaniments are not encountered in all patients with severe asthma, since it seems probable that the factor of increased pressure occurs in them during expiration It is possible that in addition to the factor of increased pressure a congenital weakness of the alveolar walls must exist before PIE arises Again, PIE may occur only when atelectasis with compensatory hyperinflation is present as well as increased pressure In the child reported by the Rosenbergs there was undue density indicating atelectasis in one part of the lung, with rarefaction indicating hyperinflation in another The X-ray picture of this patient showed air in the mediastinum and over the heart

Prolonged expiration with consequent diminution in the caliber of the pulmonary vessels (Factor B), with increased tension in the surrounding alveoli, is probably the initial factor in the production of the pressure gradient in the vessel

sheaths which leads to PIE in asthma, we do not know whether these other factors just mentioned must also be present before the alveolar base finally ruptures in these patients

The patient reported by Emerson and Beeler died apparently not of asthma but of PIE and its sequelae She had had asthma for years, and grew progressively worse, developing a partial PT, which increased her dyspnoea and cyanosis Finally, while straining to defecate, her dyspnoea and cyanosis increased markedly and she died within twenty minutes The autopsy disclosed a bilateral PT The asthma had produced the first PT, but violent straining had brought about the fatal rupture Asthma was certainly the precipitating cause but not the immediate explanation of death

Cardiospasm Another example in which forcible expiration with closed glottis resulted in increased intrapulmonary pressure until PT was produced was reported by Wood and Vinson This patient suffered from cardiospasm, and he was accustomed to fill the oesophagus with food, take a deep breath, close the glottis, and make forcible expiratory efforts The increased intrathoracic pressure caused the food to pass by the stenosed cardiac sphincter, but on one occasion this trick caused PT, probably through a primary PIE Although this patient had tuberculosis the evidence was that the disease was healed, and therefore it could scarcely have caused the PT

Blowing against Obstruction (178) Blowing of wind instruments and blowing against resistance, as when a child blows pellets out of a small tube (308) will cause SE

In all cases reported in this group, there was increased intrathoracic pressure caused by forcible expiration, with the exit for air not wholly free Polak and Adams in experiments to be recounted later, decided that in their animals it was not the increased pressure that was at fault Rupture could be prevented even with increased pressure in the alveoli, provided that expansion of the thorax was prevented In these cases of asthma, women in labor, cough, etc the thorax was not expanded beyond the depth of inspiration which preceded the expiratory effort In these cases, however, increased pressure was accompanied by decreased caliber of blood vessels during prolonged expiration It may be that increased pressure, if coupled with Factor B, can cause rupture, even though hyperinflation be absent

3 Combined with Hyperinflation Instances occur in which there is an apparent diminution in the caliber of the blood vessels, accompanied by overinflation, thus intensifying the stimulus to rupture Patients in whom the inspiratory efforts were marked, and in whom the heart was failing to keep pace with the needs of the body would combine these two factors, A and B Athletes who develop PM or PT after strenuous games would come in this category

Interstitial Emphysema after Intense Exertion Air in unusual places may occur during or after intense exertion PT is perhaps the most commonly recognized example of aberrant air in such cases, although PM has been discovered under similar circumstances (276) We would suggest that perhaps the "stitch in the side" which arises in persons not in good physical condition, when, for in-

stance, they run for a bus, is an example of localized PIE The pain is quite sudden, and severe enough to make the person cease running It has been thought to be due to muscle spasm, more recently by Capps to anoxemia of the diaphragm A logical interpretation is that the depth of respiration is greatly increased under the exigencies of running, and that the heart, not being in training, does not keep pace with the respiration in pumping blood into the pulmonary system Thus the outer circle expands as in inspiration, but the inner circle of the blood vessel does not increase correspondingly, so that the sheath is put under tension, and the alveoli rupture Air makes its way along the blood vessels, and a sharp pain results, sufficiently severe to make the individual stop running, involuntarily restrict the depth of respiration and press his hand to his side Both of the last actions aid in preventing the further stretching of the alveoli, and hence tend to make the relationships between the size of the alveolar-base circle and the circle of the blood vessel more nearly correspond to the normal We have no proof of this, but feel that here we may have true PIE in pure, restricted form

Two cases of PM are reported by Scott Both were young athletes One lad of 16, desiring to compete in a school race the following week had just completed a half mile run, when he coughed once, fell down and instantly experienced a curious sensation in his chest After resting a while he was able to go home unaided, where he at once went to bed He could not sleep, and suddenly in the very early morning sat up in bed in great distress, unable to speak When Scott first saw him a little later, he was in acute distress, with intense pain in the chest and radiating down each arm The pulse was rapid, (130) small and weak Respirations were either suspended or very shallow He presented a typical picture of angina pectoris, but because of his age and the story of the attack following exertion, PT was considered as the probable diagnosis No evidence of this was obtained, but when a roentgenogram was taken, PM was demonstrated He had several more attacks of sudden anginal pain, and in one of these his blood pressure fell from 120 to 85 mm The air remained localized in the posterior mediastinum in this boy, pressing on the aorta, thus explaining the anginal pains The anginal syndrome in spontaneous PT has been recorded in several cases (18, 29, 238) The pain arises, doubtless, from pressure of large bubbles of air on the vessels of the lungs and mediastinum (193, 195) particularly on the aorta (276)

The second case was a young man of 20 who collapsed at the end of a 100 mile cycle race with severe pain behind the sternum X-rays revealed PM Scott calls this syndrome "acute spontaneous pneumomediastinum" following the nomenclature in spontaneous benign pneumothorax, but states that he omits the word benign, "because the benignity of pneumomediastinum is at least doubtful" He cites Lord's experience of having three patients die from emphysema of the mediastinum after this complication had developed during the induction of artificial PT

Not only PM, but spontaneous PT also, may occur in athletes under circumstances similar to those in Scott's cases (166, 178, 213, 331)

There is little doubt that the PM in Scott's patients arose from an initial PIE

Such cases would seem to be relatively rare in athletes What is the explanation when it does occur? There must have been a general hyperexpansion (Factor A). Since this happens in all cases of extreme exertion, what additional circumstances might have been present to induce alveolar base rupture? Three explanations may be advanced

(1) Factor B may have been present in these cases The inspiration had probably been maximal during the racing, and the heart had probably begun to fail, as evidenced by the collapse in each case immediately at the end of the race. The alveolar bases were stretched to their maximum about the vessel sheaths, and when the heart began to fail, the blood in the vessels was not sufficient to keep the inner circle of vessel lumen expanded correspondingly A pressure gradient arose in the sheath, and the stretched alveolar bases broke Air leaked into the sheath, and the bubbles served to keep the pulmonary vessels compressed, with resulting inadequate aeration of blood The mounting CO_2 tension stimulated the respiratory center to even greater efforts, and the gasping breathing would drive still more air into the sheaths, and move along what was present toward the mediastinum In the first patient of Scott's, the exertion was not so prolonged, and the curious sensation in the chest at the end of the race may have been the initial rupture to produce PIE In the interval of time between this and the awakening in the early morning with intense retrosternal pain the air was probably making its way to the mediastinum and accumulating there in sufficient quantity to cause the anginal pains In the second case, the exertion had been so prolonged that the air had broken through and reached the mediastinum by the time the end of the race was reached, so that the marked retrosternal pain, and PM demonstrated by X-ray, were present immediately upon the final collapse

Scott noted a small thready pulse in the first boy, with rapid rate, which would indicate that there was little blood getting to the left heart to be sent out over the body The rarity of PM in athletes might be attributable to the fact that most of them go through periods of training in preparation for the final event and that this gradual training accustoms the heart to keep pace with alveolar expansion, so that the blood volume in the lungs keeps the inner circle of the sheath expanded, thus protecting the alveolar bases through prevention of a pressure gradient

The two other explanations which might account for the rare instance of PM or PT in athletes, are (2) atelectasis in some parts of the lungs permitting of excessive hyperinflation in others, or (3) weakened alveolar bases There may be a combination of these three factors.

PIE, PM and PT without Previous Exertion When the *modus operandi* of alveolar base rupture causing PIE and its sequelae is understood, it is not difficult to see how, occasionally, violent muscular exertion, predisposes to PIE. But what is the mechanism which produces PIE when there is relatively slight exertion as in walking leisurely, or standing, or sitting down? How we can explain the PT which occurs during sleep or just after awakening? The statement is made that spontaneous PT is usually found without any history of violent effort or strain (74) We will cite but a few of these cases The histories state, e g ,

that a healthy man developed either PM or PT when stepping from a train (77), or when walking onto a tennis court to enter into a game (77), while taking a shower (77), while writing on a blackboard (113), while driving a car (123, 178), while walking at an ordinary pace (113), while studying (113), etc An exciting cause or causes were probably existent, but were not discovered Even if the patient had given a suggestive history, e g , of a respiratory infection, cough, or undue exertion, the physician might not have included such a statement in the clinical history, because he might have regarded it as of no significance As physicians become aware of the numerous conditions which may precipitate PIE, they will inquire with more insight into the history of their patients for indications of predisposing factors, and the number of cases of PM and PT which are seemingly inexplicable will, we feel, be correspondingly decreased Three explanations of these hitherto mysterious cases of spontaneous PT which are not due to ruptured blebs or abscesses, to torn adhesions, to injured visceral pleura or to penetration of the chest wall, occur to us These are (1) sudden respiratory effort, (2) lapse of time between exciting cause and appearance of symptoms of PT, and (3) depressed thoracic muscle tone

(1) Sudden Respiratory Effort Weber (319) stated that 200 cases of spontaneous PT had been recorded in apparently healthy persons without any obvious exciting cause being noted beyond sudden respiratory effort In many cases, the reports do not even mention this cause, and it may not have been present

(2) Lapse of Time between Exciting Cause and Appearance of Symptoms of PT If alveolar base rupture has occurred in a relatively small area, so that air leaks through slowly, it may be a matter of hours before the air makes its way along the vascular sheaths of the lung, and accumulates in sufficient quantity in the mediastinum to produce symptoms of pneumomediastinum, or to erupt into the pleural cavity to produce pneumothorax The patient may not identify his symptoms of pain with an exertion or cough, etc , which preceded the onset of symptoms by some hours, and may therefore state that there was no exciting cause When it is understood that there may be a lapse of time between the exciting cause and the appearance of symptoms of PM or PT, as in Scott's first patient, the physician will inquire into the events of the 24 hours preceding the onset of symptoms with more care, and will often find in them the explanation of the patient's condition Thus a strenuous rugby or tennis game in the afternoon, or a race, or a workout in the gymnasium may cause the initial break-through in the alveolar bases, and the air may gradually make its way to the mediastinum The final mediastinal rupture may take place after the person is in bed asleep Long and Bray reported several cases in which some hours had elapsed after the severe exertion before the PT occurred

If a bleb ruptures, one would expect the onset of PT earlier than with alveolar base rupture The bleb is on the visceral pleura, so that with its break, air at once escapes into the pleural cavity True, the break may be small, so that the air accumulates in the pleural cavity slowly, but such a break is more likely to be of a size permitting of rapid escape than is the break in the alveolar bases More-

over, the air reaches the pleural cavity directly in the event of a ruptured bleb, and does not have to take such a circuitous route through the pulmonary and mediastinal tissues

(3) Depressed Thoracic Muscle Tone The PM or PT which occurs during sleep may be explained by the second factor just mentioned, but there is another possible explanation in such cases Henderson states that in cases of deep relaxation, (such as might occur in sleep) thoracic muscle tone is depressed As muscle activity decreases, the oxygen requirement, and therefore the CO_2 output is also decreased With less CO_2 being generated, there is less stimulus to the respiratory center, which is depressed This we know to be the case, because of the slower breathing during sleep

Henderson says that this depression of the respiratory center leads to further loss of tone of the respiratory muscles. If one is lying on one's side, the lower lung tends to become atelectatic because of loss of muscle tone, and resultant interference with respiratory movement If such underinflation were incompletely compensated for by decrease in chest wall movement, and if it invoked a compensatory hyperinflation in the other lung, alveolar base rupture might occur Such an event must be rare, because sleep occupies about a third of a person's lifetime, and very few persons experience PT during or just after arousing from sleep Should such a break-through occur, its cause may well be a composite one in which alveolar base weakening, either hereditary or acquired by disease, is an important element We feel that the explanation of PM or PT occurring during sleep is very often to be found in the period of time intervening between base rupture and irruption of air into the mediastinum or pleural cavity

Submarine Escape Training. In teaching young men to escape from submarines, the instructors take them into a diving bell to different depths in a tank of water They are then told to fasten a clip to the nose, and, with a breathing bag attached to the mouth, into which they are told to breathe in and out while going up, they ascend slowly to the surface Depending upon the depth to which they are taken, they pause at various levels, in order to allow pressure readjustments to occur between themselves and the decreasing pressure to which they are subjected as they ascend. The breathing bag has a flutter valve attachment, which permits of pressure adjustments in it, at varying depths. A number of accidents, and some fatalities, have been recorded in men undergoing this training (3, 8, 20, 33, 180, 257) In all of these cases the men have apparently become somewhat frightened and have disobeyed instructions, both as to time of pausing at the prescribed levels, and as to continued breathing into the bag. They have ascended too fast and have held their breath The result has been that the air in the lung, having no escape through expiration, remains trapped, and as the individual ascends the pressure on the chest becomes progressively less. This causes the air in the lungs to expand, with the result that there is a general overinflation These conditions resemble those produced by Griffin (113) in his dogs, except that in the latter the breath was not held, hence vessel caliber was not diminished An expansion of alveoli takes place that is too great for the alveolar wall to withstand The holding of the breath causes a reduction in the caliber of the pulmonary vessels, and the pressure gradient between alveolus and sheath is still fur-

ther heightened, increasing the opportunity for rupture At autopsy on such a patient, Polak and Tibbals found PM and large air bubbles under the pleura The air may escape not only into the vascular sheaths, but, under such extremes of expansion as those to which these men were subjected when ascending without breathing, into the capillaries as well Thus air embolism occurs, and the symptoms from this may overshadow any that might be arising from PIE The individuals usually show signs of cerebral embolism with paralyses and interference with vision, and also of air in the heart chambers, which with blood becomes churned into froth The pulse is feeble, or non-existent, the extremities are cold, and in some cases death ensues

Not only does air work its way into the capillaries, but blood from the capillaries gets into the alveoli, so that these men show bloody froth at the mouth and nose Probably in these instances, as in lung blast, as shown by Zuckerman, rupture takes place in the side walls of the alveoli as well as in the bases from too much stretching, and air in the blood vessels, as well as blood in the airway, is the result It would seem that this latter type of rupture, namely, of alveolar walls that abut against other alveoli, takes place when extremes of expansion in the alveoli, as found in submarine escape training and in lung blast, occur

Polak and Adams carried out experiments, in which they sought to reproduce the conditions of escape from the submarine bell They distended the lungs of dogs by air blown into the trachea, producing air embolism, and also PIE, as shown by large air pockets along the pulmonary vein In attempting to determine whether it was the distention of the chest or the increase in pressure which was responsible for the rupture, they bandaged the chests of the dogs before inflation was begun, and found that in such cases there was no air embolism As soon as the bandage was removed, air embolism was observed They determined this by making a trap in the carotid artery, and watching in it for the appearance of air bubbles When the chest was bandaged they could raise the intrapulmonic pressure to 80 mm Hg and get no air embolism They stated that this explains why a person can raise the intrapulmonic pressure to 100 mm Hg above normal without symptoms of air embolism, because he raises the pressure, not by expanding the chest and increasing the lung volume, but by compressing the lungs through expiratory efforts, with the glottis closed There is room here for the generalization Contracted bases are stronger, enlarged bases are weaker The strength of the base is in inverse relation to its area Stretching thins and weakens the base Although air embolism may not occur under pressures, as high as 100 mm Hg PIE may and does happen, as shown by PM, SE and PT in women in labor, children with obstructive laryngitis, etc , where pressures are probably much less than 100 mm Hg in excess of normal

When the pressure was raised to 80 mm of mercury in dogs with unbandaged chests, extensive interstitial emphysema was found in the mediastinum, posterior part of the hilus of the lungs and about the pulmonary blood vessels, which were uniformly collapsed No air was found in the lymphatics nor in the thoracic duct This is of interest in view of Boyd's statement that in the PIE of whooping cough, the air travels to the hilus by way of the lymphatic vessels

Air emboli were also found in the experimental animals in cases of local over-

inflation (188) Most patients in whom PIE is found do not show evidence of air emboli, pressure in the alveoli may have to be much higher to cause air embolism than it does to cause PIE Blumberg and Latowsky report a patient with tuberculosis in whom cerebral embolism, SE and PT occurred simultaneously.

C Cases in Which the Mode of Production of PIE is Uncertain

Lung Blast From the description of patients suffering from the effects of high explosives, only a few of which will be mentioned here (62, 120, 239, 241, 266, 304, 328), it has occurred to us that some of the patients who have lived for a time following the exposure are suffering from PIE We have published this suggestion elsewhere (199) These patients exhibit dyspnoea, cyanosis, rigid abdomen, which in some cases has been mistaken for a symptom of an acute abdominal condition, thorax fixed in the position of maximal inspiration, retrosternal pain, pneumothorax, hemothorax, blood in the mediastinum and along the vascular sheaths No one patient need, or does, exhibit all of these conditions Here as elsewhere, release of air from the mediastinum will probably relieve the pressure on the circulation sufficiently to allow the person to live long enough to absorb the air which is splinting the lung, and causing a part of the difficulty

Fullness and ballooning of the chest have been noted in victims of bomb blast who have survived We suggest that this condition was probably due to the lungs being air-locked, that is, splinted in the inspiratory position by air trapped in the pulmonary interstitium In other words, they were cases of marked PIE The writers describing this ballooning of the chest stated that it was reminiscent of emphysema Presumably they referred to chronic pulmonary or "medical" emphysema

Air has actually been found in the mediastinum, about the pericardium, at the roots of the lungs and in the subcutaneous tissues of the neck in victims of bomb blast (120) We feel that PIE and PM have occurred also in the experimental animals subjected to high explosives, for the roentgenogram in Zuckerman's figure 11 shows air in front of the heart after such treatment, and none there before Zuckerman does not mention the presence of this air

There has been a great deal of discussion as to whether the compression or decompression phase of the bomb blast has been responsible for the symptoms and pathological findings in lung blast As far as the production of PIE is concerned it seems that it could happen in either phase Zuckerman has shown that animals subjected to the compression phase alone exhibit the pulmonary hemorrhages, etc found in patients with lung blast Latner, on the other hand, has produced similar lesions in the lungs of mice by subjecting them to the low pressure phase alone In Griffin's (113) experiment on dogs, he produced PIE and PM by decompression of the chest wall, thus permitting of hyperexpansion of the air in the alveoli, with resultant rupture *There was no pressure in the alveoli of* his dogs greater than atmospheric under such circumstances It would appear, therefore, that rupture could occur during either phase after the explosion of a bomb If rupture takes place during the compression phase, the cause would be increased intrapulmonary pressure brought about by compression of the chest

wall, if it occurs during the decompression phase, the rupture is caused by alveolar hyperexpansion The duration of either phase is too rapid to permit of pressure adjustments within the alveoli, for air to be squeezed out in the compression phase on the one hand with the result that the pressure in the trapped air in the alveoli rises, or for air to be sucked back again into the lungs during the decompression phase rapidly enough to keep the lungs from being overexpanded

It is essential, of course, that the person not be killed by the blast in order to develop PIE, since leakage of air occurs only when the individual continues to breathe The tearing of the capillary walls allows blood to ooze out even if the person dies at once, so that hemorrhagic areas in the lung are a constant finding, PIE and its sequelae, PM, SE and PT are found only if the individual continues to breathe The evidence of PIE and PM may be lacking if autopsy is delayed too long after death, the air having disappeared

Lesions in the lung, similar to those found in lung blast in air, are present in persons or animals exposed to underwater explosions (299) No attempt is made to refer to all the literature on this topic In immersion blast, the abdominal lesions are the more spectacular, but pulmonary injuries, such as hemorrhages, also occur The accounts which we have read of underwater explosions have not mentioned PIE or PM specifically One of the reasons for this may be because they have not occurred in these particular cases, since the life jackets, which are usually worn in the water by those who are subjected to underwater explosions, tend to protect the thorax from the extremes of pressure changes accompanying the explosion, but leave the abdomen exposed to them On the other hand, PIE and PM may have been present, but were not mentioned because they were not as obvious as the tears in the intestines It would not be surprising, however, if PIE, PM, SE or PT were found in some victims of underwater explosions

Trauma PIE and its associated conditions may occur following trauma to the chest If the wound is a penetrating one, such as a gunshot wound (125), the PT is usually brought about by air from the outside, and the SE is found around the site of the wound rather than in the mediastinum If the lung is injured by a fractured rib, air may escape into the pleural cavity directly from the lung through the visceral pleura There are cases, however, of blunt injury to the chest in which there is no such communication between the pleural cavity and the outside air on the one hand, or between pleural cavity and the lung through the visceral pleura, on the other (322) In such instances, the air in the pleural cavity, mediastinum or subcutaneous tissues arises from an initial PIE The mechanism here would seem to be compression of some part of the chest with sudden increase of intra-alveolar pressure There might be, of course, hyperinflation in the parts not directly compressed In either event there is a rupture Kneeling on the chest (131), running over the chest with wagon wheels (241), striking the chest against some object (7, 96), may be followed by PIE, as evidenced by SE, PT, etc A physician not long ago told us of a case of his, a locomotive engineer, who fell on an icy platform, striking his chest against the corner of a station truck Extreme SE developed, and the man died in less than a day There was no rupture of the chest wall

Cooke reported nine cases of crushing injuries to the lungs Some of the patients died almost immediately, but one of them developed a tension PT In most of these, there was no tear in the pleura to explain the PT

Caisson Disease Pulver reports spontaneous PT as an accident in a caisson worker In such workers, the ascent is supposed to be made slowly, and the individual is breathing air at the same pressure as that which surrounds the chest The mechanism of PT production in this worker is not known to us since the article was not available

Hiccup Matis states in a personal communication that he is reporting a case of PM following persistent hiccup. The mechanism of PIE production is not clear in such a case

D. Cases of General Overinflation in Which a Pressure Gradient is Lacking because of Compensation by Increase of Blood Vessel Caliber

Massive Collapse If Fine and Drinker's work is correct, it would explain why PIE seldom occurs in the hyperinflated lung which compensates for massive collapse of the contralateral lung, if one is to judge its incidence by the reports of its occurrence found in the literature The entire lung is collapsed, and is receiving much less blood, this means that the other, hyperinflated lung is receiving a correspondingly greater amount of blood Although hyperinflation occurs, no pressure gradient is created because the expansion of the vascular cross-section in the hyperinflated areas compensates for the hyperinflation The sheath is much thinner between the expanded inner and outer rings but its volume is the same, therefore there is no reduced pressure in it to favor rupture of the alveolar wall Hence it does not always follow that the extent of the PIE parallels the degree of atelectasis

It must be stated here that the question of blood flow and of blood content in the collapsed lung is apparently far from settled, and one should refer to such a treatise as that of Coryllos and Birnbaum for a comprehensive resumé. Certainly it would appear to be, as many have remarked, a poor arrangement both from the physiological and pathological points of view to have the collapsed lung receiving more blood and the overinflated lung less, although such a distribution of blood in the lungs in cases of pneumothorax has been described (110), for if this were the case then the pressure gradient in an overinflated lung when the contralateral lung has suffered massive collapse should be excessive, the outer ring of alveoli being much expanded (Factor A) and the inner ring of blood vessel much contracted (Factor B) However, PM, PT and SE are seldom reported as accompaniments of massive collapse, despite the phenomenal lowering of intrapleural pressure on the affected side (119), and this circumstance argues against the idea that the blood flow to the hyperinflated lung is reduced, and that to the collapsed lung increased

Although one would not expect PT very often accompanying massive collapse, we felt that there probably were instances of this condition in which PT had occurred We are not referring, of course, to those cases of collapsed lungs in which the PT preceded and caused the collapse Sante reported a case in

which there was massive collapse followed by PT on the same side He was able to demonstrate by means of a roentgenogram a small area in the lower part of the left upper lobe that had failed to collapse with the rest of the lung He accomplished this by rolling the patient over on the side, thus bringing the inflated region nearer to the surface, because in the ordinary roentgenograms of the chest this area was concealed by surrounding atelectatic lung This area was probably overinflated, because of the following reasons When the left lung collapsed, the pressure in the left pleural cavity became increasingly subatmospheric This caused the right lung and the mediastinum to shift over to the left, as a compensatory mechanism For some reason, an area of left lung did not collapse, and it also expanded in an effort to reduce the subatmospheric pressure in the left pleural cavity But the blood supply to the left lung was reduced (92), and thus the necessary conditions for the production of a pressure gradient, (Factors A and B) were present PIE, PM and PT ensued, but even with air in the pleural cavity helping to eliminate the lowered pressure, the mediastinum and right lung still showed a shift to the left This latter fact indicates that the hyperexpansion in the right lung was not enough to compensate fully for the space left by the collapse of the left lung, so that the uncollapsed area of lung on the left was probably *hyperinflated* Thus when PIE does occur in massive collapse, it is likely to be in the hyperexpanded areas on the collapsed side, rather than from the contralateral lung

It would appear that patients with massive collapse may also suffer from PIE and its sequelae, if there are areas of the collapsed lung which are fibrosed or are adherent to the pleura, and are prevented by these means from undergoing collapse with the rest of the lung, and so are apt to spring a leak

We have encountered several other titles of articles (57, 58) to which we have not had access which suggest PT as a complication of massive collapse, although we cannot state definitely that these were true examples of massive collapse *followed* by PT

Escudero and Adams produced bilateral PT experimentally by first producing a massive atelectasis They did this by inserting lead pellets into the bronchi, or by painting the bronchial mucosa with silver nitrate until the lumen was occluded by scar tissue, after which all the air was absorbed The dogs then developed PT on the same side These authors interpreted the PT in this way With massive collapse, there was a much decreased intrapleural pressure on the atelectatic side This caused the other lung to overexpand, and air to burst through the overstretched pleura, creating a contralateral PT Then air was drawn through the mediastinum from the PT on the unoperated side to make a PT on the operated side They could demonstrate the latter occurrence by injecting air into the pleural cavity on the side of the sealed lung and could watch under the fluoroscope the development of PT on the atelectatic side They did not sacrifice their animals, and so did not [illegible] their interpretation of a ruptured pleura as the source of the air in the cavity on the sealed side The first PT in these animals was, we suggest, formed as described in the experiments on cats (188), not through rupture of the pleura but of alveolar lung

about the blood vessels in this hyperinflated lung, with formation of PM, and its rupture to produce PT.

Pneumonectomy The conditions just described for massive collapse obtain for the most part in patients from whom a lobe of a lung or a whole lung has been removed The remaining lung undergoes hyperinflation to compensate for the loss of lung volume (173) But at the same time, all the blood which had formerly traversed the whole lung field now has to pass through the remaining lung. Thus the surgeon inevitably provides against PIE in his pneumonectomy patients, because at the time that he causes Factor A to operate, namely, by producing overinflation, he also causes the blood vessels to expand in the overinflated lung, by deflecting all the blood of the pulmonary circulation through the remaining lung, and so prevents any pressure gradient from forming Hence one does not often find PIE or any of its consequences, reported after removal of a lung.

If such complications should occur, however, a careful examination of the case will usually disclose some factor in addition to loss of lung volume and compensatory hyperinflation as having been implicated Stephens reported three patients who developed PT following removal of a lung, but in each case insufflation anesthesia, under too high a pressure, seemed to be the logical cause In two patients a carcinomatous lung was removed One developed PM, SE and PT, and died the day after the operation The second developed PT during the operation, and succumbed on the table Stephens could find no tear in the mediastinal pleura in either case to explain how the air got from the opened pleural cavity of one side into the other pleural cavity We feel that the air was doubtless coming from around the hilus of the lung on the unoperated side which had experienced general overinflation and leakage of air from insufflation of the anesthetic at a pressure of 25 mm Hg It is not to be wondered at, therefore, that Stephens could not find a leak from one side to the other or even "the bronchial fistula, which surely was the cause of the emphysema " We feel that PIE explains both the contralateral PT and the SE in these cases and it is not necessary to invoke a hypothetical abrasion of the bronchus to explain the production of SE

Stephens' third patient was undergoing a lobectomy under insufflation anesthesia when the heart stopped, and, because of his experience with the other two patients, he recognized that a PT had occurred, and that this was preventing expansion of the unoperated lung The heart was massaged, air under tension was withdrawn from the unopened pleural cavity, and air blown into the good lung under pressure to make it continue to expand until the operation was over The patient continued to breathe then without forcible expansion of the lung, and recovered Stephens felt that the PT could not have arisen through the insufflation of the anesthetic, which he said was administered from apparatus which constantly controlled the pressure at 25 mm Hg We feel that this pressure might prove too high even with the thorax closed, and it has been shown (200) that the pressure necessary to produce rupture is much less if the thorax is opened, so that the lungs lack the protective support of the chest wall, than when the chest is closed.

It is interesting to learn to what a great extent the lung tissue may be removed in dogs and the animals survive Adams has shown to one of us (CCM) a dog lively and apparently quite healthy from which all but 15 per cent of the lung tissue had been removed In this animal the entire pulmonic blood must have been traversing the surviving fraction of lung, which, in this case, was the right upper lobe In one such animal, spontaneous PT developed (252)

Had the man who was shaving in the morning just finished straining at stool? What type of work had the boy just finished doing, was it anything that required tugging or lifting of heavy objects? Do the cases which come just after the patient has arisen from sleep start because of atelectasis of the lung caused by sleeping overlong in one position, with atelectasis of the dependent portions of the lung? The answers to these questions we do not know, but in the future, as clinicians become aware of the nature of the factors precipitating PIE and PM, they may inquire for these and record them more accurately

Now that pneumomediastinum has engaged the attention of clinicians, the reports of its occurrence are more frequent Meek reports PM verified by roentgenograms in a male of 27 who developed his attack following the unloading of heavy storage batteries. Monroe and Webb report it in an airman, Griffin (114) reports it in three men, two of whom had mild respiratory symptons, while the third was constantly lifting 2-lb weights In Kellogg's and Greene's patients no history was given that could account for it Lintz limits the term "spontaneous" mediastinal emphysema to those cases in which there is no demonstrable disease, atelectasis, or previous exertion to account for it. He assumes that because it can occur without presence of disease, it can likewise occur without there being any increased intrapulmonary pressure, as in the experiments recorded earlier on local overinflation But it probably does not occur without at least one of the following being present, namely overinflation, relative increase of intrapulmonary pressure as compared with that on the chest wall, decreased pulmonary blood circulation

Of course, not all people subjected to these various strains or conditions develop PM It appears that a second factor, namely, weak alveolar walls which are leak-susceptible, must be present This weakness may be a constitutional one, or it may arise through some inflammatory change in the alveolar walls In all Hamman's cases the condition cleared up, which led him to make the statement that it is benign in nature This is not always the case, however, because when the condition accompanies some inflammatory reaction as influenza (307), tuberculosis (71), asthma (89), etc , or when it occurs in the newborn, death may appear imminent or it may really occur

F Current Views on the Causes of Idiopathic Pneumothorax

We shall take occasion at this moment to discuss the current ideas as to the causes of pneumothorax simplex, or idiopathic pneumothorax We feel that many of these cases are examples of PIE followed by PM, which has ruptured to produce PT

Tuberculosis Formerly the presence of PT was regarded by some workers as *prima facie* evidence that tuberculosis was present. The prolonged rest in a tuberculosis sanatorium formerly prescribed for cases of benign PT testified to the belief that tuberculosis was the major factor in its production Hamman (122) formerly thought that most cases of pneumothorax were tuberculous in origin If PT occurred in an apparently healthy person, it was ascribed to the rupture of an adherent emphysematous bleb in a healed case of tuberculosis (320)

Gradually the repeated evidence that PT occurred in persons with no signs of tuberculosis, and who had not developed it for years after the air had been resorbed, forced clinicians to hunt for a further explanation Thus Bisenthal and Snyder found that, in twelve cases of benign PT, none had tuberculosis In only two of Long and Bray's eight patients was tuberculosis present It was present in only three of Kirshner's (159) twenty-four patients In the London Hospital, between 1924 and 1937, there were 114 cases of spontaneous PT, and only sixteen of them showed tuberculosis (251) It is now recognized that it is irrational to insist upon prolonged rest for these patients with PT who not only have no clinical signs of tuberculosis, but are actually, many of them, free of it

Sub-Pleural Blebs or Congenital Cysts When it was recognized that tuberculosis could no longer be regarded as the sole cause of PT, ruptured subpleural blebs or congenital cysts were advanced as the explanation It was supposed that these blebs, which were in communication with the airway, ruptured into the pleural cavity, causing PT Thus subpleural blebs, together with ruptured pleura became the *sine qua non* of spontaneous PT

Authors (75, 104, 109, 162) continued to assert their belief that ruptured blebs caused the PT despite the fact that in many of the cases which came to autopsy, they either found no blebs or could not demonstrate a rupture in the blebs they did find Many of these cases did not come to autopsy, and the "ruptured bleb" idea was permitted to flourish without any real proof in many instances

Stein and his associates consider an emphysematous bleb as the probable cause of the PT in the five patients whom they report In one the onset was while walking, in a second, while marching to barracks for breakfast, in a third while at rest, in a fourth while at rest after strenuous calisthenics, and in a fifth while swimming Since none of these came to autopsy, the idea of a ruptured bleb could neither be confirmed nor disproved Taschmann suggests that stenosis of a terminal bronchiole caused by the scar from a small Ghon infection may result in the ballooning of subpleural alveoli with rupture

Ornstein and Lercher assert the validity of the ruptured bleb hypothesis as an explanation of the spontaneous PT occurring in their series of 58 cases They mention that strenuous exertion preceded the onset of the PT in 23 cases, but lay the stress on the 35 cases in which no strenuous exertion was mentioned, and state that the exertion can be only a contributing cause The essential thing, they say, is the emphysematous bleb with a "check valve" which prevents escape of air They show the lungs of four persons (not these patients) with extremely large emphysematous blebs, one "as large as a grapefruit", yet none of these persons had a history of PT! Such a finding should make them examine with caution their belief that PT arises through ruptured blebs

In the case of the calf's lung (196), and in the lung of the child who had interstitial emphysema after aspirating peanut fragments into the bronchus (94), there were blebs which had not ruptured The presence of blebs does not necessarily mean that they have ruptured and that the PT is caused by air coming from them The blebs and the PT may have a common cause, namely, air in the vascular sheaths and mediastinum with a rupture in the latter Hasney and

Baum interpreted the annular shadows at the hilus of the lung of their patient as subpleural blebs at this point Evans has shown that annular shadows may indicate localized pneumothoraces, not blebs We suggest that the appearance may sometimes be due to bubbles of air in the mediastinum Cole found congenital cysts reported in only three of the eighty-two cases of bilateral spontaneous PT recorded in the literature, so that this explanation is by no means always valid Sycamore's case may have been one of ruptured subpleural bleb, the patient had suffered from PT five times, but after surgical removal of the bleb he experienced no more attacks Even here, the freedom from attacks after removal of the bleb may have been purely coincidental Gough described a patient with fatal PT, in whom a torn adhesion extended from a ruptured bulla When the lung was perfused with water, the water filled the bulla, and escaped through the tear in its surface The pressure at which the perfusion was carried out was not given

A rupture of scar tissue caused by adhesions between the visceral and parietal layers of pleura is the explanation of Acton for the PT in a man whose dyspnoea came on while resting after a days' work The type of work was not stated, but if there was an undue amount of exertion in the work, PIE, PM and PT might easily have occurred.

Congenital Weakness of Pleura When no evidence of tuberculosis or congenital cysts or subpleural blebs could be found, some authors resorted to the idea that there is a congenital weakness of the pleura in spots, and that at these areas ruptures tend to occur, giving PT (77, 159, 178, 225) The first authors (77) think that some of the bronchioles terminate directly beneath the pleura without the intervention of any alveoli If the constitutionally thin area of the pleura, or one which has worn thin through repeated rubbing against the parietal pleura, happens to be over such a bronchiole, the atmospheric air in the bronchiole causes a blow-out, and PT results If, however, the thin area overlies alveoli "in which the pressure is negligible", then the blow-out does not occur, because the negligible pressure in the alveoli is not great enough to make the pleura rupture

We cannot subscribe to such an interpretation of benign PT In the first place, at no time have we seen, in the lungs we have studied, bronchioles terminating under the pleura without the intervention of alveoli In the second place, the alveoli are always in open communication with the bronchioles and bronchi, and we cannot see how the pressure in them could be other than that in the bronchioles with which they connect In inspiration, the alveolar pressure is a little less than atmospheric, and at the beginning of expiration a little more than atmospheric, at no time could one designate it as "negligible" Congenitally thin places in the pleura, or places worn thin by rubbing, are hypothetical (friction would tend to thicken the pleura), whereas air dissecting its way along the vascular sheaths and passing out at the hilus of the lung is an actuality which can be demonstrated visually

The ability of the pleura to withstand considerable pressure has been noted even under severe strain such as occurs in paroxysmal cough or in childbirth (84),

and in many cases where there were actual blebs on the surface, there was no tear in the pleura over them (240)

Benign Pneumothorax Occurring in the Absence of Rupture of Visceral Pleura There have been those who have been willing to accept the evidence when they have failed to find ruptured cysts or blebs (171, 258, 325) Priest's patient died with a bilateral spontaneous PT with no evidence of an opening on the lung surfaces when water was forced through the bronchi, and with no sign of tuberculosis, tumor or other pulmonary disease Rossel (cited by Hasney and Baum) reported a case of hemopneumothorax in which 3500 cc of blood was found in the pleural cavity at autopsy "In spite of a very careful search, the pleuropulmonary rupture and the source of the hemorrhage could not be discovered" There was no tuberculosis

Therapy designed to cause adhesions between visceral and parietal pleurae to stop the leak in a bleb, and so inhibit further attacks of PT may be of value, if the two layers of pleura become completely adherent, in stopping air from getting into the pleural cavity, but it will be of little avail in preventing the initial leak which causes PIE, the PM that preceded the PT, or SE that may develop to relieve the PM

Why does air escape into the pleural cavities in some persons, rather than into the tissues of the neck? Why does one mediastinal pleura rupture and not the other, for the unilateral pneumothorax is much more common, fortunately, than the bilateral in man? Why does the air escape into both pleural cavity and subcutaneous tissues in some cases? The escape into the pleural cavity rather than into the subcutaneous tissues would seem to be the more common route if one is to judge from the clinical reports, especially in view of the fact that subcutaneous emphysema is recognizable without any artificial aids, whereas many small and localized penumothoraces, or even a large pneumothorax, may not be discovered until an X-ray of the chest is taken

In summarizing the evidence as to the cause of so called "spontaneous" PT, we would say that

(1) The rupture of a subpleural bleb if one is present *may* cause PT

(2) In many cases of PT coming to autopsy, there is no evidence of subpleural blebs When such blebs are present, there is often no indication that they have ruptured Therefore in such cases they cannot be the cause of the PT

(3) It is probable that the majority of cases of spontaneous PT are the result of some of the conditions or a combination thereof, set forth in this paper

(4) The lack of evidence of a precipitating cause for the PT in the clinical history is due in large measure to the failure of the physician to understand (a) what a variety of precipitating causes there might be, such as cough, strenuous exertion, mild or unobserved respiratory symptoms, etc , and (b) how long a time may elapse between the precipitating cause (such as exertion) and the appearance of symptoms This latter factor, namely, lapse of time between cause and obvious effect, doubtless explains the majority of instances in which no explanation of the PT is given

Three instances of spontaneous PT have been reported in which the first pain of

the PT occurred during the taking of a cold shower (77, 178, 302) This may have been caused by the sudden inspiratory effort usually made when the cold water hits the body, or by the strenuous exertions which may have preceded this and caused the patient to want a cold shower An unusual cause in one patient (221) was coitus She suffered from attacks of pain in the chest after each such experience, (which we think are indicative of the existence of PIE), and finally suffered a bilateral PT and died Her lungs were found covered with bullae, and throughout the lungs, large, spherical air spaces were described, which were said not to be dilated alveoli We think they may have been bubbles of air in the vascular sheaths and septa

Reitter's patient was an infant who had had a cough for several days before he suddenly became worse, exhibiting dyspnoea and definite air hunger The diagnosis was either an enlarged thymus or foreign body in the bronchus The roentgenogram showed completed atelectasis of the right upper lobe, with PT on the right Although the author does not mention it, one of the roentgenograms also, to us, shows definite air in the mediastinum, revealing that the sequence of events was probably as we have outlined it in this discussion

Vrooman reports spontaneous PT in seven persons, it came on as follows (1) while eating, (2) with no history of preceding events, (3) following an operation, (4) while diving, (5) while swimming, (6) while scrubbing a floor, (7) after intratracheal anesthesia In the last five of these cases, factors were present which could easily have induced PIE

In some of the recent literature, the tendency is to explain many of these instances of spontaneous PT on the basis of a PIE and PM, following the explanation offered (188) Thus, Griffin (113) reported a series of cases of spontaneous PT in young males One occurred while the man was running in a track meet, one while the man was boxing, receiving a severe blow on the chest, one was in a woman who was shaking a grown man violently to wake him up, the others either had a history of a respiratory illness for a few days or weeks, (4 cases) or no apparent illness or violent exertion to account for the PT, (3 cases) Griffin's experiments in which he produced PM, PT, SE, etc , in experimental animals by placing them in the decompression chamber, with a tracheotomy tube in place extending outside the chamber have already been recounted

G Idiopathic Pneumothorax

Recurrent Pneumothorax Simplex. Although most of the cases reported are of patients who have had only one attack of PT, there are instances (13, 43, 77, 128, 209, 225, 228, 298, 317) in which there were repeated attacks, some patients having as many as fourteen In practically all of these, there was no evidence of tuberculosis One must postulate a constitutional tendency to rupture In this connection it is of interest that in the cases cited above in which PT was recurrent, three were found in which it also was familial (13, 225, 228)

Bilateral Pneumothorax Occasionally in man the air goes into the two pleural cavities simultaneously (1, 32, 39, 50, 63, 84, 102, 127, 128, 143, 154 (4 cases), 166, 201, 207, 217, 221, 222, 224, 232, 258, 263, 271, 314, 315, 317, 321, 327, 329)

Most of these patients succumb because of extreme limitation to respiration, but some have survived We have not attempted to collect all cases of bilateral PT, because the same explanations hold that are true for unilateral PT Once the mediastinum is distended with air, it is astonishing that it so seldom ruptures on the two sides Grant describes a region in the posterior mediastinum, between the oesophagus and the aorta, in which the two layers of mediastinal pleura are in apposition A rupture at this point would put the two pleural cavities into communication The pleura here evidently is resistant, preventing this accident from happening oftener In some animals there is said to be a normal opening between the two pleural cavities, so that all pneumothoraces would be bilateral in these forms, unless the opening were plugged with exudate, or adhesions In other animals, such as the cat, the layer of mediastinal pleural separating the two pleural cavities is very thin, so that when it ruptures, air enters both pleural cavities simultaneously When PT in man is caused by the rupture of a bleb, a unilateral type only is expected, unless the tension becomes so high in one pleural cavity that it breaks through secondarily into the other side When PT is caused by a rupture in the mediastinum, the effect may be uni- or bi-lateral

Sergent (see 127) considered bilateral cases as due to tuberculosis, but Rossel (see 127) pointed out that bilateral spontaneous PT is rare in sanatoria Lamont thinks it likely that the air gets into both pleural cavities simultaneously, because he says that a unilateral case rarely becomes bilateral This further supports the idea that the initial rupture is from the mediastinum Richmond's patient, who had died with a bilateral PT, had two areas in the right lung, about 5 cm in diameter, "markedly distended with air" The upper left lung was similarly distended with air, being held to the chest wall with adhesions These two areas, unable to collapse with the rest of the lung, probably produced PIE and permitted even more air to escape into the pleural cavities

The Hereditary Aspect Spontaneous PT probably occurs far more frequently than the reported cases in the literature would indicate, but is probably not so common that it is experienced by many people at some time in their lives Most women do not have SE when in labor, most asthmatics do not suffer from PT simplex, there possibly must be in addition to the exciting cause, an inherent weakness in the alveoli themselves, and perhaps in the pleura as it is reflected over the mediastinum Liverani, also Lorge, postulated a constitutional factor in spontaneous PT The first weakness permits of rupture of the alveolar bases into the underlying connective tissue, and the second of PT, or the other complications of PIE

If the weakness happens because of some pre-existing disease, then its occurrence in several members of a family may be looked upon as coincidence, unless there was an hereditary susceptibility existing to the disease which caused the weakness If the weakness of the alveolar walls or of the mediastinum or of both be of constitutional character, one might expect to find occasional records where several in a family are affected The following cases of familial incidence were encountered father and son (11, 228) (the son in Muller's case having had three spontaneous pneumothoraces), two brothers (165, 167, 225) (one brother in

Morawitz's family had two attacks), two persons in the same family, (326, 336), five persons in the same family (105), father and daughter, one with two, and the other with three attacks (13), several in a family (204)

This weakness, whatever it may be, has been designated as a weakness of the lungs, but Morawitz says that it should be called a "pleura weakness" (Pleuraschwache) because it is the pleura over the bleb, usually resistant, which must rupture The weakness is probably rather in the alveolar wall which permits of the first rupture into the vessel sheaths, and in the mediastinal pleura which allows the second rupture into the pleural cavity

The fairly numerous reports of spontaneous PT on the opposite side occurring during the artificial induction of PT, and of bilateral spontaneous PT, would indicate that there may be a point of weakness in the pleura as it reflects over the mediastinal contents, which ruptures in these PT cases In most of the familial incidences reported above it is specifically stated that there was no tuberculosis, or other pathological condition in the lung, to explain the PT.

Artificial Pneumothorax. There have been reports in which spontaneous contralateral PT, PRP, SE, etc , have been produced as a result of the induction of an artificial PT There are two ways in which the complications might arise: (1) the air injected into one pleural cavity might rupture into the mediastinum, and from thence traverse the paths it takes when it occurs in the mediastinum from PIE (188), or (2) it might enter the mediastinum from the interstitial tissue of the lung, in the way already described Inasmuch as the lung which is being collapsed artificially is a diseased lung, uniform diminution in size is unlikely, and hence local overinflation may be found in the areas remaining uncollapsed. Cases in which PM (76), SE, PT, PRP occurred during the induction of an artificial PT have been recorded (6, 12, 15, 151, 245, 277, 327) Joress's patient suffered from abdominal symptoms sufficiently severe to make abdominal operation seem imperative In a second case, withdrawal of air relieved the abdominal pain In our experimental animals it was not possible to induce PM and SE by injecting air into the pleural cavity A rabbit failed to develop PM and SE when air was injected in one pleural cavity under a pressure of 2 cm Hg , and a cat failed to show PM and SE under similar circumstances, when the pressure was 12 cm Hg (188). Both animals, however, developed contralateral PT.

Smith (285) reported bilateral PT as a complication of induced pneumoperitoneum Air was being injected for visualization of mesenteric lymph nodes The woman became dyspnoeic, with pain in the chest The flow of air was stopped, and later recommenced She collapsed and died shortly after Smith reports that "A number of small holes were discovered in the diaphragm connecting the peritoneal with both pleural cavities" One wonders what the holes were, and if the air did not really traverse upward through the connective tissue about the aorta and oesophagus over the same route which it follows when air in the mediastinum goes down into the retroperitoneal tissues

Pneumohemothorax Sometimes the PT is accompanied by hemorrhage into the pleural cavity In the animals with experimental PT not only was air found in the sheaths of the blood vessels but sometimes blood also, which had oozed in

from the torn capillaries at the base of the alveoli (188) Thus blood might escape along the same pathway which the air had followed, and just as the air pathway had remained obscure and unobserved in most cases, so the pathway of the blood was not easily apparent Perry (250) in 1938 reviewed the literature and found nineteen cases, and added two of his own Some recovered after the withdrawal of the blood and air, and others died There were eight autopsies from this group, and in three, ruptured adhesions were found, in two others, bullae were discovered which were assumed to be the site of the bleeding, and in three others there was no point of bleeding to explain the hemorrhage In some of the cases (178, 296), even in those in which ruptured adhesions were present, the bleeding point could not be demonstrated in them as was true in Perry's own case The blood would be oozing probably from the posterior part of the mediastinum in these cases, and its source would be difficult to locate

Maxwell's patient had been doing work which involved severe strain, and suffered from PT for 48 hours before the blanching of the skin called attention to the fact that a hemorrhage was occurring

Hurxthal reported a case in which a man had been doing strenuous tugging at the cushion of his car when he experienced a sudden sharp pain in the right shoulder He became pale and dyspnoeic and had abdominal pain Examination revealed a PT, and both air and blood were withdrawn, with great relief to the patient He had suffered from colds for some time before this accident In this patient, there may have been atelectasis followed by PIE and its accompaniments, or there may have been severe strain, with the breath held and increased intrathoracic pressure, followed by rupture, or there may have been a combination of the two There is adequate explanation for the occurrence of the PT and hemothorax in this patient Of Staffieri's three patients there was also a history of exertion in two, (1) climbing stairs and (2) struggling with an insane man In the third there was a history of fractured ribs to account for the bleeding

Tannenbaum's patient had a mild cough for months before hemopneumothorax developed Housden's patient had a history of cough for nine years followed frequently by pain in the chest which the patient had called "muscular rheumatism" and for which he had never sought relief, as it cleared up in a few days One night he had an excessive fit of coughing, and the pain became so severe that he had to go to bed Three days later, when he was straining at defecation, the pain increased sharply and he became faint He died a few hours after and was found to have both air and blood in the pleural cavity Although there were some blebs on the surface of the lung, no point from which either air or blood could have come was found

Two of Hopkins' patients also had an apparent reason for their hemothorax. One had been suffering from an acute respiratory infection, and a few days later choked on a piece of meat and coughed excessively He at once felt a pain, became dyspnoeic, and was found to have hemothorax The second patient had a severe cough and fever, and developed a hemothorax The third case developed his while shaving, and no history of a preceding condition which [illegible] explain it

was mentioned by Hopkins The latter statement is also true of the patients of Beaumont, Birch, Falla, Hartzell (3 cases), Snively et al Castex and Mazzei (45) report a case of hemopneumothorax

Doane's case is of interest, because it would appear that the cause of death in this instance was definitely the pneumomediastinum, and not the hemorrhage from the punctured lung This woman had several ribs fractured in an auto accident There was a left hemopneumothorax, while there was also evidence of air over the precordium She began to recover slowly, but four days later suddenly became pale, cyanotic, showed air hunger, and died When the sternum was removed at autopsy, a gush of air escaped from the mediastinum which was filled with air bubbles Although there was a massive hemorrhage in the left pleural cavity, the account would indicate that death was due to the pressure of air in the mediastinum.

In cases of hemothorax which come to autopsy, a search should be made for the presence of blood in the vascular sheaths, to determine whether there has been an alveolar rupture with leakage of blood as well as of air The mere presence of a torn adhesion of the surface of the lung, which may have been lacerated at autopsy, should not be assumed to be the source of the bleeding until it can be proved unequivocally to be so

Thus it seems clear that the phenomenon of the escape of blood mixed with air, from the alveoli into the underlying pulmonic connective tissue, as found in the experimental animals (188) has been duplicated in clinical cases in which the blood and air even go so far as to invade the pleural cavity.

Pneumoretroperitoneum It has been recognized that this condition is an accompaniment of spontaneous or artificial PT, and also that the air dissects its way into the retroperitoneal spaces In cases where the peritoneum does not rupture, and allow air to escape into the peritoneal cavity, the term pneumoperitoneum is a misnomer, for the air is retained behind the peritoneum, not within the cavity In the experimental animals this was a constant accompaniment of the PT and SE So much air accumulated that the kidneys were elevated completely from their beds of fat and lay floating on huge vesicles of air

In order to follow the course of events, the abdomen was opened in one animal and the diaphragm exposed before the insufflation of air was begun Air was then introduced as usual into the lower lobe of the right lung, and the sequence of events noted The right dome was depressed into the abdominal cavity as the overdistended right lung pushed against it This continued until the alveoli ruptured and the air dissected its way to the mediastinum, thus relieving the pressure in the right lower lobe The middle of the diaphragm then bulged, and almost immediately air began to appear in increasing quantities in the retroperitoneal tissues This continued for some time when suddenly both domes of the diaphragm, which had been exhibiting respiratory movements, bulged far down into the abdomen and respiratory movements ceased This was taken to represent the moment when the mediastinum ruptured, causing a bilateral PT under pressure This pressure was found to be above atmospheric when a needle attached to a mercury manometer was thrust into the pleural cavities This se-

quence of events might be altered somewhat in the unopened animal, where the restraining effect of the intact abdominal wall would influence the amount of air going into the retroperitoneal spaces before final rupture of the mediastinum occurred

In some, perhaps in all, of these cases, of PM with either or both conditions of PT and SE, air will be found in the retroperitoneal tissues, and still further hinder, by its upward pressure, the movements of the diaphragm, thus increasing the respiratory distress, and pressing also, no doubt, upon the abdominal blood vessels, so further impeding the circulation

In view of the large amounts of air found in the retroperitoneal spaces of the experimental animals, it is not surprising that the presence of air in these regions, and sometimes free in the peritoneal cavity, might cause so much pain that a mistaken diagnosis of an acute abdominal condition might be made Steigmann and Singer reported three cases of their own and found four others in the literature in which acute abdominal symptoms indicated opening the abdomen Muller and Mogavero's patient was operated upon for supposed rupture of gastric ulcer which was not found Others (18, 237) also referred to abdominal pain in patients with PT They attributed the pain to that referred from the PT, but there seems to be enough pulling on the ureters, for example, when the perirenal tissues are distended, to permit of the interpretation that the abdominal pain is not referred but local in origin

In spontaneous PT the air is already in the mediastinum, and has no trouble dissecting down the oesophagus and aorta as they pass through the diaphragm In the case of pneumoretroperitoneum occurring in the course of artificial PT, Banyai (15) points out that the air introduced into the pleural cavity makes its way along the mediastinal structures and into the retroperitoneal spaces Eisen reported air about the kidneys in a child suffering from SE and PT, following the impaction of a coin in the oesophagus

Ehrlich (78) reported a case of renal operation with insufflation anesthesia in which retroperitoneal air was disclosed upon opening the abdomen This was interpreted as due to an abrasion of the pharynx, as the pressure at which the anesthetic was administered was controlled at 25 mm Hg In this patient, before the abdomen had been opened, the retroperitoneal air preceded the SE, so that the abdominal route of escape may be more common than the cervical one The reverse of this route has been reported (16), when air appeared in the mediastinum after having been injected into the peritoneal cavity PM was produced in a patient in whom air was injected into the rectum for a double contrast enema (34) No lesion was found in the rectal mucosa by which air escaped but there must have been a tear in the alimentary tract at some point

Tension Pneumothorax In not a few of the cases of spontaneous PT the air in the pleural cavity is under a pressure higher than atmospheric A "valve vesicle" has been held responsible for this It is alleged that this mechanism permits air to escape into the pleural cavity, but not to get out of it Such a conception is necessary, of course, for there must be a one-way flow, otherwise no pressure could be built up in the thoracic cavity Unfortunately, however, many

writers, in discussing tension PT, have assumed that air escaped into the pleural cavity by way of the valve vesicle *during inspiration*, and was prevented from getting out because the valve closed *during expiration* A few citations will be made here to show that this is a prevalent idea Norris and Landis stated "In most instances the tissues in the immediate vicinity of the perforations act as a valve which permits the air to enter the pleural cavity during inspiration and as the respiratory movement is reversed the valve closes so that no air can escape As a result, air accumulates in the pleural cavity under pressure".

Chandler stated "With every inspiration, air comes out through the valvular tear into the pleura, with every expiration the valve closes and the air is imprisoned in the pleural cavity" Ellison and Carabelli stated "Forceful inspiratory effort, as in crying, pumps enough air into the pleural space to exert a positive pressure during the inspiratory phase of quiet breathing" These quotations are typical of many found in the literature (275) Gas does not contravene the known laws of physics, merely because there is a "valve vesicle" present. Let us set out the undisputed facts in logical order, and there can be no doubt as to the conclusion

(1) Air will *not* flow from a point of lower to a point of higher pressure, but *will* flow from one of higher to one of lower pressure

(2) Air does flow into the pleural cavity from the lung, either directly or indirectly by way of the mediastinum, to produce pneumothorax

(3) Therefore, to produce pneumothorax, the pressure in the lung must be higher than that in the pleural cavity

(4) Air in the lung can never be under a pressure greater than atmospheric during the phase of inspiration, inasmuch as the lung is open to the atmosphere

(5) Air in the pleural cavity can be under a tension much higher than atmospheric

(6) Therefore, air does not escape from the lung through a valve vesicle into the pleural cavity during inspiration, once the pressure in the pleural cavity reaches atmospheric It does escape during inspiration until the pressures are equalized on both sides of the pleura

(7) Air in the lung can be under a pressure much greater than atmospheric during the phase of expiration, as in cough, or when the glottis is closed, and strong expiratory efforts are made as in defecation, or when strong efforts have to be made to *expel* the air from the lung, as in asthma, stenosis of the airway, etc

(8) Therefore, in all cases in which the air in the pleural cavity is under a pressure at least equal to that of the atmosphere, all further additions of air in the pleural cavity occur only during the expiratory phase

We may conclude therefore, that *air enters the pleural cavity which is under a pressure greater than that of the atmosphere, only when the lung is in the act of a forced expiration*

Novak and Churchill recognized this fact and stated, "If pleural adhesions are present, the tear on the surface of the lung in spontaneous pneumothorax is kept open and air is forced into the pleural cavity by coughing and forceful expiratory effort, thus building up a positive pressure in pneumothorax". We feel safe to

say that one does not develop a tension PT unless there is a cough or a forced expiration of some sort Thus, in Elghammer's patient a tension as high as 48 mm Hg developed, and 21 aspirations had to be performed before the pressure fell to and maintained itself at the proper level There was a history of very severe coughing It is true that not all accounts of tension PT mention the severe cough, straining movements or forced expiratory efforts, because they have failed to realize the significance of these for the development of tension PT When it is understood, these forced expirations will be recorded in such histories The air, of course, will flow from lung to pleural cavity during inspiration in the beginning, until both are at atmospheric pressure, but after that will not go from lung to pleural cavity except during *expiration*

Tension PT may be caused by PIE as well as by ruptured blebs on the pleura, and therefore it is dealt with here It is evident that tension PT can develop only in the event of the exciting cause still continuing, as it would in cases of asthma, foreign body with cough, etc With forced expiration, more air would be blown into the vascular sheaths, make its way toward the mediastinum and from thence escape into the pleural cavity If the tissues prevented the return of air from pleural cavity to mediastinum by means of a one-way valve, a tension PT could be built up with each succeeding forced expiratory effort Relief of this excess pressure is of course imperative

Pneumoprecordium In the experimental animals (188) air extended forward around the heart, between the layers of pleura and pericardium The same thing happens in man When the heart contracts it is enveloped by a blanket of large air bubbles, with the result that there is a loud crepitation which has been given various descriptive terms, including "pericardial knock" Many authors have called attention to it Lister, in 1928, reported this sound in a patient who had PT, and Hamman (123, 124) described it in a series of seven patients It may sometimes be heard some feet away from the patient, to his alarm and that of his family

The air has usually been thought to be in the pericardial sac, but in the experimental animals, except in a single recent case, it was outside it Busni, to whose article we have not had access, described pneumopericardium in a patient who had bilateral spontaneous PT Not all patients with spontaneous PT develop air over the heart, if one assumes that air in this location is accompanied by pericardial knock, for the latter is so unmistakable that the patient is certain to mention it If the air is present in a large amount it would tend to press upon the heart, and upon the coronary vessels, and so further impede the circulation

H Obstructive Emphysema

There is a type of emphysema known as obstructive, in which a bronchus is partially but not wholly occluded by some object such as a foreign body In inspiration the lumen of the bronchus widens, thus allowing air to get past the obstruction into the lung behind it In expiration the bronchial lumen narrows, and closes about the object, thus blocking the exit Some observers have held that such a mechanism permits of the building up of a pressure higher than at-

mospheric in the occluded portion of the lung thus distending it (31), others have affirmed that it builds the pressure up to atmospheric, so that air then continues to ebb back and forth past the obstruction, the pressure being the same on both sides (179) It is difficult to see how any interpretation other than the latter could be correct, for air, like all fluids, flows from points of higher to those of lower pressure It is true that in the occluded region the pressure would rise above that of the atmosphere on expiration—that is, if the air in the region involved had no escape by way of the pores into the surrounding lung substance—and this pressure rise would be particularly evident after *forced* expiration, but the pressure would again drop to atmospheric as the next full breath was taken, and the elevation of the ribs and the descent of the diaphragm enlarged the volume of the thorax, and as the lung behind the obstruction was again in communication with the atmospheric air

Although the pressure is not raised above atmospheric by such an obstruction, in inspiration, it is possible to increase the *volume* of that lung up to the point of maximum inspiration, as is shown by figure 7 of Biennemann It might be asked why, with this maximal distention, rupture of the alveolar bases does not occur, and PIE result That question cannot be answered unreservedly, but it would appear that in these cases, although there is hyperinflation, so that external Factor A is operating, there is probably a dilatation of the blood vessels in the lung, thus keeping the volume of the vessel sheaths constant PIE does not appear in obstructive emphysema, if one is to judge by the description of clinical findings in this condition

III DISCUSSION

No attempt has been made to refer to all of the literature which indicates that PIE as judged by the presence of its sequelae has been present Representative papers have been reviewed, and these, for the most part, are recent Most published explanations of the phenomenon of air in the mediastinum we believe to be incorrect, but deference is due to those writers who, lacking the key to the route of this air from the lung, nevertheless recorded their observations accurately Special tribute should be paid to those American physicians who, during the critical influenza epidemic of 1918–1919, although they had little time for anything but the care of their patients, yet nevertheless put down their observations for the use of their fellow scientists

While we have attempted to describe the varying disease conditions in which aberrant air has actually been found, it may well be that we have not noted all in which it may be present, and thus it is more than probable that, in the future, it will be encountered in cases not yet mentioned as exhibiting this complication *Atelectasis of a part of the lung*, whether that atelectasis arise through failure of the lung to expand at birth, through blocking of the airway by some substance foreign to the body, or by a growth or by mucus or pus in the airway with resorption of air, or through crushing forces which collapse part of the lung, indeed atelectasis, no matter what its cause, may act as a trip-hammer to set off the train of events leading ultimately to the invasion of the interstitial tissues of the

body by air from the lungs *Depletion of blood in the streambed of the pulmonic vascular system*, combined with (1) hyperexpanded alveoli, or (2) excess pressures in the alveoli, is the second mechanism favoring escape of air from the alveoli into the interstitial tissue of the lung, particularly the vascular sheaths *Increased intrapulmonic pressure alone may cause rupture*

This, then, is the theme, the principal *motif* of this paper, that *pulmonic interstitial emphysema and its sequelae—air in the mediastinum, peritoneal cavity, subcutaneous tissues, pleural cavity—are present in many conditions, differing widely in their causes, their clinical manifestations and in their seriousness, but all having a single common factor of pressure gradient between alveoli and vessel sheath, and hence an opportunity for air to gain access to the interstitial tissues of the lung*

There are two accessory themes, as follows (1) *the presence of this "pneumapathy" or air sickness, is usually unsuspected and its manifestations are often regarded as part of the disease syndrome* Thus in pneumonia, or in any acute inflammatory process in the lung, one might consider that all the dyspnoea and cyanosis are caused by the lowered area of respiratory surface exposed to the oxygen But in a pneumonia which involves only a lobe of one lung, or less than a lobe, there is probably more available space for taking up oxygen than the patient needs Let us suppose, however, that PIE occurs It is in the *hyperinflated* area that the rupture occurs, that is, in the very region that is supplying the air therefore, it is in the part attempting to carry on oxygenation that the vessels are most likely to be compressed Much more of the lung is useless for gaseous transfer, then, than would be indicated by the area involved in the consolidation

The more extreme the dyspnoea, the more likely is air to pass from alveoli to sheath, and therefore, the more likely to compress the vessels still further, and to exaggerate still more the pressure gradient existing between the circle of alveoli and the vessel lumen As the air travels to the mediastinum, it exerts pressure on larger trunks whose smaller branches might not have been encroached upon by the air When it finally reaches the mediastinum and presses upon the large veins entering the heart, venous return is interfered with not only from the lungs, but from the entire body, so that stasis and cyanosis supervene These manifestations may be, indeed, not a part of the acute infectious process, but of air in the interstitium of the lung

This assumption that part, at least, of the dyspnoea and cyanosis of patients suffering from a pneumonic process is caused by interstitial air compressing the pulmonary and mediastinal vessels, rather than altogether by lung consolidation, is justified by the experience of Torrey and Grosh, who found that the dyspnoea and cyanosis lessened materially when the mediastinum ruptured and air escaped into the subcutaneous tissues of the neck The relief of dyspnoea and cyanosis in the newborn when air was removed from the mediastinum by a needle (116, 117, 283) shows that PM can be responsible for these symptoms

In this connection an interesting report was made over 40 years ago by Ewart and Roderick concerning a child who had died of diphtheria They found extensive mediastinal and subcutaneous emphysema, and thought that death was

due to "cardiac and pulmonary embarrassment set up by the increasing distention of areolar tissue of the anterior and posterior mediastina and the roots of the lungs" The heart had stopped in systole, which they considered to be due to the fact that the pressure of the surrounding lungs prevented the relaxation of diastole They distinguished between the emphysema around a tracheotomy wound, which they called "inspiratory" emphysema, and that found in their patient, which they designated "expiratory" emphysema, since they thought that it was caused by the violent coughing of the patient As we pointed out before, the emphysema which occurs in the presence of a tracheotomy wound may have the same cause as the emphysema which occurs before tracheotomy, so that it too, may be "expiratory" in origin

The experimental work of Humphreys, Moore and Barkley also confirms this idea that the dyspnoea, cyanosis, failing heart of the patient in diseases involving inflammatory reactions in the respiratory tract may be dependent upon PIE and PM and their effects rather than upon the initial disease They studied pulmonary pressures during inflation of the lungs of dogs They found that the mere presence of these distended lungs in the thoracic cavity so presses upon the heart that it is prevented from filling with blood, hence from sending out blood to the lungs We would add that as the vessels fill less and less with blood, a pressure gradient is created, or the steepness of the gradient already created by the hyperdistention of the perivascular alveolar bases is heightened, and rupture may occur The air in the vascular sheaths then compresses the vessels, so that even should the heart be capable of sending out blood into the lungs, the lumen of the vessels is too compressed to admit of much blood entering The hyperdistention which at first was caused by excess air *within the alveoli*, now is continued, even after cessation of inflation of the lungs, by air *within the interstitium*, so that the heart continues to be compressed Collapse of the lungs during expiration becomes difficult or impossible, hyperinspiratory efforts are made to draw new air into the lungs, thus assisting in still further heightening the pressure gradient and continuing the leak The dyspnoea, cyanosis, failing heart in such cases would be caused not by the pneumonic process, but by the presence of aberrant air

The only externally visible manifestation of this condition is the subcutaneous emphysema The next most frequently diagnosed sequel of pulmonary interstitial emphysema is pneumothorax, and this, if small, goes unrecognized without the aid of roentgenograms Since both of these conditions are probably far less frequent than air in the mediastinum, and that, in turn, probably less frequent than air in the interstitial tissues of the lung, we feel that the latter condition occurs far more often than its presence is suspected

Not only may the effects of PIE and PM be misinterpreted, and be regarded as the symptoms of the disease responsible for the PIE and PM, but *they may simulate heart disease*, in persons in whom the PIE and PM may be present as independent clinical entities, not accompanying any other disease. Thus in healthy persons in whom the aberrant air is the result of strenuous exercise or sudden respiratory effort, the pain caused by the air in the mediastinum or in the

pleural cavities may so simulate heart disease that a mistaken diagnosis is quite possible Master, Kalter and Dack report spontaneous pneumothorax in a patient in whom all symptoms pointed to acute coronary occlusion The changes in the electrocardiograms were suggestive of myocardial infarction, with abnormalities in the precordial lead consisting of inversion of the T-wave, and a very small or absent initial positive deflection These workers stated that these alterations were probably due to rotation and displacement of the heart caused by air in the pleural cavity Roentgenograms revealed the PT, and with the absorption of air, and re expansion of the lung, the electrocardiographic tracings returned to normal

We have referred to the fact that PM causes anginal pains, and it may be that the electrocardiogram in PM unaccompanied by PT might show similar deviations from the normal We have not seen such observations recorded We emphasize that PIE, PM and PT may erroneously be diagnosed as heart disease, and should be thought of when a history of anginal pain is elicited

The presence of PIE and its sequelae may be unsuspected or incorrectly diagnosed as an *acute abdominal condition* when the air has escaped into the retroperitoneal spaces Acute abdominal symptoms, especially when somewhat obscure as to their cause, may be caused by PRP When exploratory laparotomy has been performed, and no lesion found to explain the symptoms, PRP should be suspected A roentgenogram of the chest before the operation, or of the abdomen, would yield the correct diagnosis in such cases

This brings up the point of the *value of the roentgenogram* in the diagnosis of PM Its value in PT has already been recognized Although PM can be diagnosed by the peculiar crunching sounds in the chest which are synchronous with the heart beat, (provided that such sounds are present, of course), the absence of these sounds does not preclude the presence of PM It may merely be that the air bubbles are not in the mediastinum at a level at which they can be pressed upon by the beating heart If SE does not occur to indicate that PM is present, the latter may go unrecognized, unless proof of its existence is furnished by a lateral roentgenogram of the chest The usual antero-posterior view is usually of little value in the diagnosis of PM since the presence of air behind the sternum is obscured by the bony structures in front of it The lateral view will reveal the presence of air in the mediastinum whether behind or in front of the heart, and also in the superior mediastinum above the heart In patients in whom the history is at all suggestive of the possibility of PIE and PM being present, (the numerous diseases and conditions in which PIE and PM may be found have been outlined in this paper) lateral roentgenograms of the chest should be made, either to confirm or exclude the diagnosis of air in the mediastinum

The second accessory theme of the paper is this *pneumomediastinum, which in the majority of instances is dependent upon a preceding pulmonary interstitial emphysema*, has been regarded as always of benign nature, the only danger being that the physician is likely to give too grave a prognosis We wish to emphasize, from the evidence presented in this paper, both experimental and deduced from clinical records, that this condition *is to be regarded as potentially serious*, because

[illegible] PIE or PM [illegible] 114, 116 [illegible] 229 231 [illegible] 234. Most of these [illegible] or four years when children have be[illegible] of the presence of PIE or PM. As [illegible] will appear dealing with air actually demonstrated in th[illegible] or at autopsy, or in the vascular sheaths and con[illegible] of the lung at autopsy. Clinicians will know under wh[illegible] this syndrome, and will prevent it when possible or de[illegible] if it has occurred.

Although life may be saved in many instances by the withdrawal of air fro[illegible] the mediastinum, or from the pleural cavity when it is under tension there, th[illegible] patient may die (4). An accumulation of adverse circulatory and respirator[illegible] may prove too severe for the patient, unless the condition is relieve[illegible] early.

If attack, as well as PIE, is present, that is, if the air in the interstitial tissu[illegible] in holding the lung locked in a position of inspiration, one might question wheth[illegible] volume of air from the mediastinum alone would suffice to weight the scales [illegible] favor of recovery. Although removal from the mediastinum of its contained a[illegible] might not release air caught in the septa, the partial relief of pressure on the hea[illegible] and vessels might well be sufficient to tide the patient over until the air in the se[illegible] tissue could be reabsorbed.

It has been noted that in persons in whom PIE or PM is present there is a f[illegible] in blood pressure. This may be the result of several factors acting alone, or t[illegible] pathway (1) the venous congestion on the systemic side brought about by t[illegible] limited respiratory movements, and by the compression of the pulmonary arter[illegible] and veins preventing blood getting into the left side of the heart, (2) the [illegible] ability of the heart to fill owing to the distention of the surrounding lungs co[illegible] [illegible] and to the pressure upon it of bubbles of air in the mediastinum, a[illegible] (3) the rise of the pressure in the mediastinum. Rolleri and Francis found th[illegible] the blood pressure falls as the pressure in the mediastinum rises.

[illegible] as to how much compression of pulmonary vessels can sust[illegible] without a fatal outcome. Children, Rochlaen and Turnbull included the p[illegible] 50 per c[illegible] without altering

arterial or venous pressures When 60 to 85 per cent of the artery was occluded, the cardiac output fell as did the blood pressure Obstruction of more than 85 per cent of the cross section of the artery always proved fatal

A number of points still have to be investigated How much does the pressure in the mediastinum have to be above its normal level to rupture into the pleural cavity? How great a variation in this respect exists between various species, and between individuals in the species? What pressure has to exist in the mediastinum before air dissects its way into the cervical fascia? What pressures are safe in administering an anesthesic when the thorax is intact, when the thorax is opened? Does the degree of difference between air pressure in the alveolus and in the supporting tissues necessary for rupture differ at varying pressure levels? For example, if when the pressure on the chest wall is atmospheric, and that within the alveoli is 25 mm Hg above atmospheric, rupture were induced, would the gradient still have to be 25 mm Hg or more, or less, when the intra-alveolar pressure was atmospheric, and pressure on the chest less as in Griffin's dogs? Does the pressure gradient have to be less steep when an infectious process is present than when the lung is not pathological? Does the age of the patient make any difference? Does the sex of the patient make any difference? Do males show spontaneous PT far more often than females because there is an inherent difference between the sexes in susceptibility to rupture, or do males make more violent expiratory efforts in strenuous work? Women in childbirth probably make much greater efforts than most men in their work Does the pressure gradient which induces rupture of the capillaries into the alveoli have to be steeper than that which induces rupture of air into the vascular sheaths? If so, how much steeper? These and many other questions about the problems of PIE and PM remain to be settled

IV SUMMARY

There are many clinical cases in which the presence of air in the tissues of the lung is not suspected, and in which its effects have been regarded as being produced by the primary disease itself, rather than by the interstitial air There are many other cases in which air is recognized as being present in the pleural cavities, in the subcutaneous tissues of the neck, trunk, etc , in the retroperitoneal spaces or in the peritoneal cavity, but in which the method of escape of air and the route it followed is misunderstood Because this air in the pulmonary interstitial tissues may cause death through airblock, if it is not removed, the clinician must become aware of the conditions which predispose to its appearance These conditions may be divided into three categories (1) those in which there is first an atelectasis of some part of the lung, followed by hyperinflation in adjoining regions of the same lung or in the opposite lung, (2) those in which there is a general overinflation with or without increased intra-alveolar pressure, (3) those in which there is evident a decreased blood supply to the pulmonary vessels preferably either with increased intra alveolar pressure, or with hyperinflation

The mode of escape of air is the same in these three classes, namely, through ruptured alveolar bases into the sheaths of the pulmonary vessels, and the clinical

picture may be the same in all, with any of the following conditions either alone or in combination air in the mediastinum, in the thoracic cavity, in the subcutaneous tissues of the face, neck, chest, axillae and body, in the retroperitoneal spaces from whence it may rupture into the peritoneal cavity, around the pericardium, in which event a pericardial knock is heard There is dyspnoea and cyanosis when the pressure in the mediastinum rises too high, limitation of respiratory movements with the chest becoming fixed in a position of maximal or submaximal inspiration when the air either distends the mediastinum, or gets into the connective tissue septa of the lung The air may gradually be resorbed, and the patient recover, or it may increase in severity and the patient may die

The precipitating cause of this train of events may occur in a wide variety of conditions, but is always a pressure gradient from air in the alveoli to perivascular sheath or underlying septa, leading to alveolar rupture and formation of pulmonary interstitial emphysema.

Air leaks from the overstretched alveoli into the sheaths or adventitia of small branches of the pulmonary arteries and veins, (Factor A), or from alveoli, surrounding blood vessels not filled to the normal extent with blood, (Factor B), the alveoli being either normally expanded or hyperinflated, under atmospheric pressure or pressures above atmospheric The bubbles of air press upon the vessels occluding their lumina producing airblock, and may leak into the interlobular connective tissue, causing airlock

It makes its way along the vessel sheaths to the mediastinum, where it presses upon the large vessels at the base of the heart It may be removed from the anterior mediastinum

It may make its way upwards into the neck, face and axillae, thence down over the chest and arms, giving rise to subcutaneous (erroneously called "surgical") emphysema

It may make its way downwards along the aorta and oesophagus into the retroperitoneum, and may rupture into the peritoneal cavity Symptoms produced by air in the abdominal cavity may simulate acute abdominal conditions for which operation may be mistakenly performed

It may make its way forward over the heart, whence it may give rise to a loud crunching sound, "Hamman's sign", with each heart beat

It may travel laterally into the vessel sheaths of the other lung, or backward along sheaths of the same lung into areas in which there is no leakage

It may rupture the mediastinal wall producing pneumothorax Collapse of the lung tends to stop the leak, except in cases in which there is violent cough

Tension pneumothorax may result from air escaping from the mediastinum, but the tension is built up not during inspiration, but during forced expiration of cough or when the glottis is closed and the intrapulmonary pressure rises above atmospheric

Air continues to leak as long as the factor initiating the original break is operative In some instances, the leak appears to be favored merely by respiratory movements, especially if they are of a dyspnoeic character

The factor responsible for moving the air along the sheaths is the lengthening and shortening of the bronchi in normal respiration.

Pain may possibly be caused by air pressing upon the pulmonary and mediastinal vessels, simulating angina pectoris

Circulation is interfered with by the collapse of the pulmonary vessels producing airblock, causing venous stasis, and giving rise to cyanosis

Respiration is interfered with by the splinting action of the air in the connective tissues of the lung causing airlock, preventing the escape of air in expiration and giving rise to dyspnoea

The heart action may be interfered with in three ways (1) by being pressed upon by the distended lungs which prevent its filling, (2) lack of blood to fill it, because of systemic and pulmonic venous congestion, arising through pressure by air bubbles on vessels, and stasis, and (3) by direct pressure upon it by air bubbles in the precordium, and in the posterior mediastinum

Factors predisposing to leakage are apparently toxins of certain infectious diseases, particularly influenza, and perhaps an inherited constitutional weakness of the alveolar walls

Once the leakage has begun, the pressure necessary to continue the leak need not be so high as that initiating the rupture

When air escapes from the mediastinum into the subcutaneous tissues, or into the retroperitoneum or even into the pleural cavities, provided that it does not produce a bilateral pneumothorax, or a tension pneumothorax, the condition is likely to be benign, since the pressure in the mediastinum is relieved If the leak continues, and builds up higher pressures in the mediastinum than can be relieved by the avenues of escape, the condition, originally benign, may become malignant

It is when the air cannot escape from the mediastinum and the pressure rises too high that the condition becomes malignant

Air in the mediastinum and interstitial tissues of the lung may be occult, unrecognized by means of visible manifestations It accompanies a wide variety of clinical conditions and respiratory diseases

Especially when it is occult it may be malignant, when it is malignant it can be fatal

When its presence is diagnosed, it may be withdrawn, and thus the patient's life may be saved

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It is a pleasure to record our satisfaction with the excellent facilities of the library of the Medical School of the University of Western Ontario without which this paper could not have been written

BIOLOGIC FALSE POSITIVE SEROLOGIC TESTS FOR SYPHILIS

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I. INTRODUCTION

Since the independent discovery in 1906 by Wassermann, Neisser, and Bruck (296) and by Detre (54) of the complement fixation test for syphilis, and the subsequent development of flocculation tests which bear the name of their originators, reliance upon these tests has passed through several phases. At first they were used only to confirm clinical diagnoses, and there developed an extensive literature on the diverse conditions which were considered to cause the positive tests encountered in patients without clinical evidence of syphilis In view of the clinical nature of syphilis, however, with its asymptomatic stages, latent syphilis could never be excluded in such cases As laboratory performance was improved, physicians gradually developed so much reliance on the tests as to regard them as the primary basis for diagnosis, to be supplemented by clinical evidence The tests were applied on a wide scale in serologic "dragnets" to detect unrecognized cases, and even became the legal basis for the diagnosis of the disease in many premarital and prenatal laws In the last decade, however, the pendulum has swung back again It is being increasingly recognized that a serum which is positive even to a variety of procedures does not necessarily prove the presence of syphilis.

Although Scandinavian workers have reported during the last decade the occasional development of transient false positive tests in a variety of diseases, in America the importance of this problem has been brought to the foreground only during the last four years by Dr J E. Moore and associated workers at the Syphilis Clinic of the Johns Hopkins Hospital (76, 77, 215, 217, 219) Evidence has been presented (214) that transient false positive tests may appear even in the absence of demonstrable disease, and in some cases may persist for a long time The social stigma attached to syphilis causes a psychological trauma which obviously demands considerable effort to avoid an erroneous diagnosis. Besides, a positive test in a candidate for induction into the armed forces of the United States may be the basis for rejection, and the acquisition of syphilis by military personnel is severely penalized The possibility of an appreciable incidence of false positive reactions in apparently healthy individuals is therefore a matter of military importance. The Committee on Medical Research of the Office of

Scientific Research and Development has consequently organized in several universities a search for differences between true and false positive sera This review is written in connection with such a project

Discussion of biologic false positive tests is complicated by the fact that the serologic tests for syphilis do not furnish uniformly reproducible measurements Since the reliability of these tests is of great importance to the public health, there have been a number of evaluation studies to stimulate improved standardization and performance and to eliminate the less reliable procedures The Health Organization of the League of Nations held such conferences in 1923, 1928, and 1930 A number of surveys which have been held in the United States since 1935 will be discussed later As a result of these surveys the reliability of the tests has been greatly improved, many inadequate procedures have been discarded, and standards of performance in state laboratories have been raised Even with present improved standardization, however, there is still considerable instability of the sensitivity of a given procedure, so that conflicting reports between different laboratories, or between successive tests in the same laboratory, are frequently encountered with syphilitic sera of borderline reactivity In view of the possibility of excessive sensitivity, as well as the possibility of clerical errors, a single positive report cannot be considered valid evidence of syphilis or of a biologic false positive reaction

With these considerations in mind, it is obvious that many cases which have been reported as biologic false positives were undoubtedly technical false positives In this review reference is made to very few papers written before 1930, when adequate standardization had not yet become widespread As far as possible, all reports since that date are noted which are concerned with false positive tests in various diseases, although much of even the modern work was performed under less than ideal conditions An effort is made to distinguish the more reliable reports, but the incidence of false positive reactions in various pathological conditions will ultimately have to be inferred from the mass of evidence from a variety of sources The numerous conflicts among reports on the incidence of false positive tests in various conditions are largely a reflection of the variation in sensitivity of the tests as performed in various institutions [2]

For a discussion of earlier serologic results and of technical details the reader is referred to Eagle's monograph (71) Kolmer (173a) has recently reviewed the problem of false positive tests

II INCIDENCE OF FALSE POSITIVE TESTS

1 *Criteria of Diagnosis*

The clinical literature presents wide variation in the criteria used for establishing a case as false positive Unfortunately, arbitrary serologic criteria, based

[2] While the evaluation of flocculation tests of strictly defined procedure is complicated by variation in sensitivity of lots of antigen, the complement fixation (Wassermann) tests provide confusion doubly compounded (121) Although there are well standardized complement fixation tests (Eagle, Kolmer), most laboratories report complement fixation tests simply as "Wassermann tests" or "modified Wassermann tests" which vary from one laboratory to the next in the preparation of the antigen and in every possible detail of performance

upon discrepancies between various kinds of tests, have often been used This practice must be strongly condemned, since syphilitic as well as false positive sera may show such discrepancies (207). A purely serologic criterion of another kind may be used as the basis for diagnosing false positive cases—those which are positive to one or more types of test but which become negative after a few weeks or months without antisyphilitic treatment Such transient reactions are usually associated with acute infections. The reliability of these cases depends on the reliability of the laboratory which performs the tests and upon the demonstration of *more than one* positive blood specimen (preferably to more than one kind of test or to the same test in two different laboratories) before the tests become negative, in order to eliminate the suspicion of technical or clerical error. The necessity of demonstrating repeatedly positive reactions has been more consistently recognized in the Scandinavian than the American literature

Exclusive dependence on transient reactions, however, will probably not detect all cases Much more difficult to evaluate are the positive reactions which persist for long periods of time without evidence of syphilis The criterion here must be primarily clinical rather than serologic, the reliability of the diagnosis being proportional to the adequacy of the history and physical examination which fail to provide evidence for syphilis As Stokes has stated (quoted in 219), "(there are) instances in which one Wassermann test will convict a laborer over his own denial, two will make a case against a banker or a railroad president, but three successive positives will scarcely convince the medical adviser of the 'guilt' of a clergyman." Most of the papers to be discussed below omit consideration of persistently positive cases, and undoubtedly frequently err in the other direction by including technical false positives

2. U. S. Evaluation Surveys

Original Methods Evaluation Surveys were held in 1935 (47) and 1941 (240) by the Committee on Evaluation of Serodiagnostic Tests for Syphilis, composed of representatives of the U S Public Health Service and the American Society of Clinical Pathologists A large number of authors or representatives examined by their own procedures 200 or more sera from patients in various stages of syphilis, and sera from patients with diseases known to give rise to false positive tests (leprosy, malaria), from normal individuals, and from various types of patients in whom the presence of syphilis had been excluded as completely as possible "Sensitivity" refers to the percentage of positive tests obtained in the syphilitic cases, "specificity" to the percentage of negative results in the non-syphilitic cases

In addition, since 1936 annual surveys have been carried out for the purpose of establishing standards of laboratory performance Syphilitic and normal sera were tested by the authors of seven approved tests and by a number of state and other laboratories which use these tests The standards set for approval of a laboratory were that its results should be not over 10% less sensitive than the originator's results with a given test, and the specificity should never fall below 99 0% The results of these surveys have served as the basis for altering from

year to year the preparation of the antigens in order to reach the goal of maximum sensitivity without falling below 100% specificity

In Table I are presented the summarized results obtained by the originators of these seven tests in the various surveys These values were recalculated according to the system in use since 1940, in which doubtful reports are credited or penalized with one half the value of the positives, specificities were determined on normal sera The variations in apparent sensitivity from year to year are of no significance since the syphilitic population tested varied in each study, but comparison of the various tests within a given study shows rather marked variation in sensitivity Thus the Kolmer complement fixation test was distinctly less sensitive than the flocculation test in the first two surveys, giving rise to

TABLE I

Specificity and Sensitivity of Serodiagnostic Tests in U S Serologic Evaluation Surveys

	KOLMER		EAGLE C.F		KAHN STD		KLINE DIAG		EAGLE FLOC		HINTON		MAZZINI		REF
	Spec.	Sens	Spec	Sens	Spec	Sens.	Spec	Sens	Spec	Sens	Spec	Sens	Spec	Sens	
1935*	100	77 4	—	—	99 8	82 5	100	79 3	97 2	84 5	98 9	88 6	—	—	(47)
1936	100	59 5	100	85 8	100	76 5	98 8	91 3	99 0	77 8	100	90 2	—	—	(237)
1937	100	88 2	—	—	100	85 5	100	88 9	—	—	99 5	93 9	—	—	(238)
1938	100	78 4	100	74 7	100	72 8	100	76 7	100	78 8	100	84 1	—	—	(110)
1939	100	83 4	100	75 7	100	81 6	99 5	83 3	100	84 0	99 0	87 4	—	—	(110)
1940	100	71 7	100	66 1	100	71 2	97 2	75 7	99 5	78 0	100	79 7	—	—	(†)
1941	100	78 5	98 8	80 7	100	79 2	100	76 0	98 8	85 4	99 2	84 3	99 2	86 9	(239)
1941*	100	74 1	100	59 2	100	62 2	99 4	62 6	100	72 1	100	65 8	100	78 6	(240)
1942	100	84 9	98 8	84 9	100	80 7	100	83 1	94 7	92 0	100	89 1	99 6	89 8	(241)
1943	100	82 0	100	73 9	100	71 8	100	65 6	100	80 7	100	84 7	100	81 2	(†)

Calculated to give half value to doubtful reports
* Original Methods Survey
† Unpublished results

the impression that flocculation tests were inherently more sensitive In subsequent studies, however, the complement fixation tests equalled the flocculation tests in sensitivity

The data on specificity are very satisfactory, most of the tests showing 100% specificity each year with normal sera With ill rather than normal non-syphilitics, however, as tested in the more comprehensive Methods Surveys (47, 240) (not presented in the table), most of the tests show 0 2–0 5% more non-specificity than with normal subjects These data on cases of tuberculosis, cancer, fever of various origins, jaundice, and pregnancy are significant since they are more representative of the hospital populations which are subjected to routine testing

Many laboratories perform a variety of tests other than those approved, the results of a number of these are presented in the reports of the Methods Survey (47, 240), but they need not concern us since they are rarely encountered in the literature In Europe the Sigma, Sachs Georgi, Meinicke, and Müller flocculi

tion procedures have been widely used, but we have no way to compare their specificity with that of the tests listed in Table I

The incidence of false positive tests, when performed under optimal conditions, thus appears to be very low, but there are two reasons why one cannot conclude from these data that the problem is statistically negligible First, the committee chose as non-syphilitic controls cases which offered no reason to suspect syphilis—which would automatically exclude (except in the leprous and malarial groups) cases which were positive to several or all of the tests Secondly, as was emphasized by Kahn (143), a high specificity is deceptively reassuring, since the number of non-syphilitics tested in routine hospital admissions or other dragnets is so much higher than the number of syphilitics Hence, in a population of which 5% were syphilitic, a test with 99 5% specificity and 80% sensitivity would give 0 5% false positives and 4 0% true positives If the diagnosis were made on a serologic basis alone, one ninth of the cases treated would therefore not have syphilis.

3 General Incidence

(a) *Incidence in Normal Individuals* The only large scale study of the incidence of presumably false positive serologic tests in normal individuals is that of Eagle (72), who collected the results of tests on 40,545 students in a number of colleges The procedures used in the various institutions were not given Of the 73 positive and 117 doubtful cases only 40 were positive and 22 doubtful on retesting, 21 of these 62 cases were diagnosed clinically as syphilitic and 5 had had treatment which may have been based only on serologic grounds The remaining positive and doubtful cases represent an incidence of 1:1,250 By statistical analysis of the high correlation of these presumably false positive tests with the incidence of proven syphilis in certain schools, Eagle inferred that approximately 70% of these positive reactions were probably syphilitic, leaving an incidence of biologic false positives of only 1.4000 He concluded that " the incidence of such reactions would appear to be sufficiently small to justify, as a general public health measure, the diagnosis of syphilis in clinically normal persons giving repeatedly positive serologic tests, even in the absence of clinical evidence or history of syphilitic infection It must be emphasized, however, that this conclusion is valid only for the particular group of young, normal, white adults here studied "

In the individual case, however, exception to this rule may be taken, as was pointed out by Mohr, Moore, and Eagle (214) They reported nine patients who were considered to have exceptionally reliable histories excluding the possibility of latent syphilis These were followed for 1–3 years, during which time they remained clinically normal and in four cases reverted to seronegativity. These authors now have several dozen persistently positive cases which are being followed without treatment (personal communication) The justification for withholding treatment from such patients will be considered in a later section (IV-2)

(b) *Incidence in Hospital Populations* As was shown in the Evaluation Surveys, the incidence of false positive tests is appreciably higher in hospital patients than in normal individuals The 0 42% false positive Hinton tests in 21,073 cases reported by Crawford and Ray (45) were probably largely technical false positives, since most of them were negative on retesting in Hinton's own laboratory, while many biologic false positives were undoubtedly missed by arbitrarily considering as syphilitic any case in which the positive Hinton test persisted or was verified by a positive Wassermann test Clifton and Heinz (42) reported 1 46% transient positive or doubtful Kolmer, Eagle, or Kahn tests in 5,625 infants and children Only one-sixth of these reacted in more than one of the 3 tests, and the authors unfortunately do not state what proportion were negative on retesting This type of information was furnished in the report of Hill (120), who found 0 43% single positive or doubtful Hinton or Davies-Hinton tests in 26,700 children, but only 0 14% which were repeatedly positive and then became negative within one week to nine months without treatment The majority of these had some acute or chronic infection *It was not stated that any* of the persistently positive tests were considered false, although it might be expected that it would be easier in children than in adults to exclude the presence of syphilis

In the Scandinavian literature, Forssman (85) reported 0 13% false positive Kahn or Wassermann tests in 7,711 hospital admissions, and Eldh (78) reported 0 25% false positive Wassermann reactions in 20,798 medical patients Krag reported that only 0 027% of 70,000 (180), and subsequently 0 04% of 120,000 (181) cases were false positive This very low incidence may be due to the stringent criteria used—that the reaction be strongly positive to both Kahn and Wassermann tests, or weakly positive to at least three of the 5 tests used for a recheck, and that the reactions all become negative within seven seeks All these papers probably furnish too low an estimate, since they consider as false only very transient reactions The cases listed, however, are reliable since all were positive more than once before becoming negative

4 *Incidence in Various Diseases*

(a) *Yaws (Frambesia), Pinta, Bejel* These diseases are caused by spirochetes morphologically almost indistinguishable from *Treponema pallidum* and share many of the clinical characteristics of syphilis The positive serologic tests which occur quite regularly in these infections may therefore be considered true, rather than biologic false positives

(b) *Leprosy* This disease has long been known as a cause of persistent false positive reactions, but is statistically of little importance in this country Badger (3) reviewed the 24 papers on the subject which appeared before 1931, most of which reported a high incidence of false positive Wassermann tests He noted 20 2% positive Wassermann and 27 5% positive Kahn reactions in 207 patients in a leprosarium in Hawaii, which was approximately three times the incidence of positive tests in a non-leprous hospital serving the same population Some of the cases had a very high titer Kahn test when quantitated

Fifty leprous sera were included in the 1935 Evaluation Survey (47) and were separately discussed (108) The incidence of positive reactions among the five tests varied from 40% with the Hinton to 72% with the Eagle flocculation test. A striking illustration of the degree to which the sensitivity of the unstandardized early tests varied, rendering the early literature practically valueless, is the observation that the Kolmer test produced 64% positive reactions, although shortly after its introduction Kolmer in 1923 (170) reported no positive reactions among 125 lepers

Similar results on leprous sera were obtained in the 1941 Survey (240), in which it was also found that Eagle's spirochetal antigen was no more specific than several of the tests employing the usual beef-heart antigens, although Eagle and coworkers (74) and Capelli (35) had noted considerable superiority of spirochetal antigen Spirochetal antigens will be further discussed below.

Several reports from countries in which leprosy is common confirm the observation that biologic false positive tests are quite frequent in this disease (25, 35, 129, 224, 276) although this has been denied in one report (231) No clear correlation has been noted with the severity or type (dermal or neural) of the disease

(c) *Malaria* This disease raises a consideration which will have to be borne in mind in evaluating biologic false positive tests in all acute infections—namely, that the incidence varies markedly with the frequency with which the blood is tested In the 1935 Evaluation Survey (47) 36 non-syphilitic patients in various stages of malaria gave 11–19% positive results with the various tests A more extensive study of 266 patients by the same committee (109) found only 4–9% positive and doubtful Hinton, Kline diagnostic, and Kolmer tests Eller (79) also noted a moderate incidence of positive tests in inoculated malaria

It was shown in Italy (81), however, that practically all of a small series of 10 cases of malaria inoculated developed a positive Wassermann test at some time during the disease if tested every few days, in one case the reaction lasted as long as six weeks Similar results were reported by Kitchen, Webb, and Kupper (161) in 25 inoculated cases which were tested twice weekly, all developed some degree of reaction in the Kahn or Wassermann test, 21 being positive to both The maximum incidence occurred at 3–4 weeks after inoculation, but in a few cases the reaction appeared even before the onset of clinical symptoms Eagle et al (75) and Burney et al (32) similarly found some degree of transient reaction to the Wassermann test or Eagle flocculation test in nine of eleven cases inoculated with Plasmodium vivax It should be emphasized that these studies were oriented toward finding by frequent testing the maximum incidence of false positive tests, and hence included many weak reactions Of the 100% transient positive reactions reported, only 10 to 20% were of a degree which could lead to diagnostic confusion

An incidence of 5–20% transient positive serologic tests on hospital admission of naturally occurring malaria has been reported by several observers (51, 282, 305), most of the reactions were weak There is no reliable evidence that false positive tests occur during the latent stage of chronic malaria Since the

positive tests occurring during the acute stage are all reported to disappear within a few weeks, the diagnostic problem does not seem to be serious, except in the occasional case which develops the positive test before the full-blown clinical appearance of the disease (51)

Several workers (197, 266, 272) concluded that malaria does not cause biologic false positive reactions inasmuch as the incidence of positive tests was found to be no greater in malarial than in non-malarial hospital patients These data were obtained, however, in tropical countries where syphilis, yaws, and leprosy affected up to 50% of the population, so that the malarial false positive reactions were lost amid the other positive tests

Eagle and coworkers (75) were unable to confirm the conclusion of Nagell (227) that the complement fixation test with spirochetal antigen was much more specific than the ordinary Wassermann test in malaria

Fischer and Gunsberger (84) concluded that the false positive reaction in malaria is due to antibody to destroyed red blood cells, since an alcoholic extract of human erythrocytes fixed complement with these sera just as did Wassermann antigen from beef heart, whereas a special extract of beef heart purporting to be low in erythrocyte content was much less reactive with malarial sera Their description of the preparation of this special extract fails to substantiate the claim that it was relatively free of erythrocyte extractives, and their data offer no support for their conclusion as to the origin of the antibody Drogeloh (57) observed that malaria transiently increased the serologic titers of syphilitics, and interpreted the results as indicating the operation of physical rather than immunological factors

It is concluded that false positive tests occur quite regularly in the acute stages of malaria but the majority of these are weak and very transient

(d) *Infectious Mononucleosis* (*Glandular Fever*) Considerable interest has been shown in the false positive serologic tests occurring in this disease since the report of a case in 1928 by Lohe and Rosenfeld (199) It has been emphasized (199, 263) that the adenopathy, fever, and rash of infectious mononucleosis complicated by a false positive serologic test may be difficult to differentiate from secondary syphilis Fortunately the reactions in infectious mononucleosis are usually very transient and weak, whereas those of secondary syphilis are found to be of high titer if quantitated

Kolmer (174) has compiled the published reports and found a total of 191 cases subjected to a Wassermann test, of which 20 9% were positive at some time, and 146 cases subjected to one or another flocculation test, of which 11 6% were transiently positive The actual incidence of transient positive reactions is undoubtedly considerably higher than these figures indicate, since in many reports the blood was tested only on admission, whereas the reactions usually appear after a week or more of the disease (263) It is important to realize, however, that a false positive reaction may appear early in the disease and is sometimes observed on hospital admission, especially since the patient may not enter the hospital until several days have elapsed during which the illness was considered a cold or grippe The highest incidence reported was in a series of 27

cases in the London epidemic of 1930 (96), of whom sixteen had a positive or doubtful Wassermann test during the first 3 to 4 weeks of the illness, and a somewhat smaller number had positive Kahn or Sigma flocculation tests Bernstein (18) reported transitory positive Wassermann or Eagle flocculation tests in eight of 44 cases, most of whom had weak reactions, although two cases (17) developed a complement fixation titer of 1·64

The numerous reports of small groups of positive cases (86, 107, 156, 174, 248, 265, 298, 299, 300, 303), do not necessarily indicate that the incidence is extraordinarily high in infectious mononucleosis, since until recently this disease has been something of a diagnostic triumph and hence has enjoyed a low threshold of publication Sadusk (262) reported a case in which the Wassermann and Kahn tests remained positive for six weeks Failure to obtain any positive reactions was reported by several investigators with small groups of cases (33, 128, 213) and by Halecrow (104) who tested "many" patients in a large epidemic of 296 unusually mild cases Such diverse results are probably explained by variation in sensitivity of the tests and in the frequency of testing the patient after the onset of the disease, although the possibility of variation in the strain of the infectious agent cannot be excluded The two persistent cases of Radford and Rolleston (250) were probably syphilitic, since other members of the family were also positive.

It has been suggested that the false positive Wassermann tests encountered in infectious mononucleosis may be related to the heterophile antibody to sheep cells which regularly appears in this disease, since antisheep cell hemolysin (amboceptor) is a reagent in the Wassermann test. Conclusive evidence against this as an important factor is furnished by the following considerations: 1) flocculation tests are also frequently positive, although anti-sheep cell hemolysin plays no role in these, 2) there is no correlation between the heterophile antibody titer and serologic tests (18), and 3) absorption of a few such sera with sheep cells has removed the heterophile antibody without appreciably affecting the serologic tests (18, 107, 174).

Bernstein's suggestion (16) that the false positive serologic tests for syphilis in this disease are part of a general non-specific antibody stimulation is vitiated by the fact that at least some of the cases showing a high agglutinin titer to the typhoid group had previously received typhoid-paratyphoid vaccine. He also emphasized the much greater number of false positive Wassermann than flocculation tests in infectious mononucleosis This has not been confirmed by other workers

(e) *Vaccination (Variola)* The discovery in 1940 (5) that vaccination causes false positive serologic tests is of particular interest because of the mass immunization associated with military mobilization Studies on groups of 100 to 263 individuals tested at intervals after vaccination have been reported by three groups (83, 200 and 201, 203) They found that 11 8–16% of the patients reacted to one or more tests at some time A few of these persisted for as long as three months, but most of the tests in all three studies were plus-minus or 1 plus, and would have been considered negative in a routine laboratory report Al-

though the danger of erroneously diagnosing syphilis after vaccination is real, only 2 3% (203), 4% (200), and 5% (83) of these series ever showed a 3 or 4 plus reaction to any test, and few of these remained positive when retested a week or two later The maximal incidence appeared to occur at about two weeks after vaccination A reported failure (9) to obtain a positive Kahn test in 100 patients was probably due to the long delay (29 to 76 days) before testing

Arthur and Hale (2) reported that of 94 soldiers tested at weekly intervals starting three weeks following vaccination, 14 8% reacted at some time to the Kahn test, and some of these were also positive to the Wassermann test, only 6 3%, however, were positive on more than one occasion Most of these were weak reactions Since these men received typhoid, tetanus, and yellow fever inoculations at about the same time as vaccination, it is impossible to assign the reaction to any one of the procedures It is particularly important to avoid such a false diagnosis in the Army because of the severe penalties involved Thomas and Garrity (283, 284), apparently excluding doubtful reactions, found only 0 26% positive Kahn tests in 10,000 naval recruits tested "on the average 12 days after vaccination," in contrast to the 0 06% in 10,000 tested before vaccination

(f) *Trypanosomiasis* Experimental trypanosomal infection of rats and rabbits was early reported to cause positive Wassermann (189) and flocculation (192, 193) reactions These experimental results, however, do not indicate that human infections with trypanosomes would necessarily be accompanied by positive serologic tests, expecially since the rabbit is so prone to develop these reactions that the tests are often positive even in normal rabbits The reviewer has been unable to find any references to false positive results by modern serologic tests in clinical trypanosomiasis within the last decade Kelser (157) has developed a diagnostic complement fixing antigen of the organism of Chagas' disease (*T cruzi*) and stated that "Tests of numerous Wassermann-positive sera indicate that no difficulty will be experienced from cross reactions in connection with the two diseases "

(g) *Rat-Bite Fever* Because of a rough morphological resemblance between *Spirillum minus* and *Treponema pallidum* the serologic reactions in this disease have been followed with some care, although it was discounted as a source of false positive reactions by Bayne-Jones in 1931 (10) For a more recent bibliography the reader is referred to the paper of Brown and Nunemaker (29), which critically reivews the American cases reported up to 1942 and presents an altered conception of the etiology of this disease They point out that adequate proof has been obtained in relatively few cases that the etiological agent was *Spirillum minus* (*Spirochaeta morsus muris*) Of 17 definitely spirochetal cases found in the American literature since 1930, 10 had a positive Wassermann or flocculation test Beeson (13) has recently reported two more cases due to *Spirillum minus*, one of which had several weak Kahn tests, unfortunately there was no followup on the infant or testing of its parents to prove that it was not syphilitic There is no question that this disease can produce false positive reactions (309, 281a)

Brown and Nunemaker further present evidence that some cases of rat-bite fever are caused by an entirely different type of organism, *Streptobacillus moniliformis* (*Streptothrix, Haverhillia moniliformis*) Of 8 serologically tested cases collected from the American literature in which this organism had been recovered from the patient's blood by culture on special media, three had positive tests for syphilis. Since one of these probably had congenital syphilis, the only biologic false positives were the two laboratory infections of Dawson and Hobby (52), in which no followup was reported to see whether the reactions were transient. Brown and Nunemaker added 8 cases of their own in which the diagnosis was made by culture or by detection of antibodies to the streptobacillus in high titer. A transient positive serologic test was obtained in only one of these, in which the diagnosis was not established with certainty. On the basis of only the two proven cases of Dawson and Hobby we cannot conclude that biologic false positive tests occur with any frequency in this disease, a decision will have to await the more numerous cases which will probably be discovered as the new bacteriological and immunological methods are more widely applied In a large milk-borne epidemic of streptobacillus infection (246) serologic tests were unfortunately not reported.

False positive serologic tests in rat-bite fever of undefined etiology have been reported recently by several authors (26, 120, 215).

It is concluded that false positive tests occur quite frequently in rat-bite fever caused by *Spirillum minus* (Sodoku fever), but inadequate information is available on cases caused by *Streptobacillus moniliformis*

(h) *Relapsing Fever* This disease, which is caused by several species of spirochetes (*Borrelia*), is very rare in United States Tsun and Chung (287) reviewed the earlier literature, consisting of seven conflicting reports, and reported that 7 of 88 Chinese cases had transient positive Kolmer, Kahn, or Kline tests, most of them being positive to all three tests In addition 29 other cases were persistently positive and were therefore considered syphilitic, although eleven of these had no evidence of the disease It is not clear that these were followed long enough to rule out the possibility that some were false positive reactions. Parr (233) reported that seven of fourteen cases had a positive Wassermann reaction which became negative after the disease was cured by small doses of arsenicals Murrell (226) presented a transiently positive American case. It appears that relapsing fever is frequently accompanied by a positive serologic test for syphilis.

(i) *Kala-azar* It is impossible to state whether leishmaniasis causes false positive serologic tests for syphilis, since the laboratory work in tropical countries is, in general, not adequately standardized and the chronic nature of the disease prevents the application of the criterion that the reactions be transient Greval (99, 100, 101) believes that the incidence of positive Wassermann tests in patients with kala-azar in India exceeds the incidence of syphilis in the population; this is disputed by Lloyd (198).

(j) *Tuberculosis.* While it is clear that tuberculosis does not give rise to a positive serologic test for syphilis in any large proportion of the cases, even a small

percentage of reactions would be of significance in so widespread and chronic a disease Whether such reactions exist is a matter of dispute In the 1935 Evaluation Survey (47) the percentages of positive reactions in 53 cases were Hinton 5 7, Kolmer 2 0, and Kahn, Kline, and Eagle flocculation 1 9% Parran and Emerson (236) reviewed six earlier papers, most of which failed to find evidence of false positive reactions, and presented the findings of an official committee established to study this problem Of 458 supposedly non-syphilitic sera furnished by nine sanatoria, eight were positive to most or all of the Eagle, Hinton, Kahn, Kline and Kolmer tests performed in the laboratories of the originators These were threfore automatically considered syphilitic, although four gave only "probable" evidence on reexamination, three could not be reexamined, and one gave no evidence whatsoever In addition sixteen gave a positive or doubtful result in one or more of the tests, although repeat specimens gave only three positive or doubtful results It was concluded that "tuberculosis toxemia may contribute a confusing factor to syphilis serology It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures" The equivocal result of such a study, using the best technical facilities available, illustrates the difficulty of proving a definite but low incidence of biologic false positive reactions, because of the temptation to assume that a specimen positive to a variety of tests is probably syphilitic

The strongest case for the production of false positive reactions by tuberculosis was presented by Dunner and Mayer (60), who found that 2 6% of 1,200 pulmonary cases without evidence or history of syphilis were positive to one or more of several tests Twleve of these were autopsied and presented no pathological evidence of syphilis, on the other hand, during the same period five cases with a history of old syphilis also were without signs of the disease at autopsy Warring (294) found 106 positive or doubtful Wassermann, Kahn, or Kline tests in 2,160 cases of tuberculosis, the arbitrary criteria of falseness render this study valueless Berg (15) found an incidence of only 3 55% positive Wassermann tests in 13,239 tuberculous adults, which makes it clear that the incidence of false positives must at most be quite small, since the incidence of syphilis in the corresponding white American population might be expected to approach this value Sweany (280) reported that in 1,000 autopsies of patients dying of tuberculosis, pathological signs of syphilis were found in one third of the 4 1% of patients with a positive Wassermann reaction Inasmuch as negative autopsies are not unusual in old syphilitics, he concluded that there is "no reason to warrant the suspicion that tuberculosis causes any more than an insignificant number of false reactions" With this the reviewer agrees

(k) *Pneumonia and Other Respiratory Infections, Atypical Pneumonia* Although pneumonia was not recognized in the older literature as a source of false positive reactions, within the past decade there has been considerable attention devoted to this problem in Europe Of the fifty-two transiently positive Wassermann tests noted by Eldh (78) in 21,000 cases, twenty six had pulmonary disease, including ten cases of pneumonia (out of 1,014 cases of the disease) and three of

influenza (out of 548 so diagnosed). A number of cases of pneumonia and other respiratory infections with repeated but transient positive reactions have been reported by other Scandinavian workers (22, 85, 160, 180, 181, 225) and elsewhere in Europe (95, 131) Lindau (196) noted ten transiently seropositive cases of respiratory infection, including four members of one family suffering from "bronchitis" It has been suggested (95) that such reactions in pneumonia might be related to the herpes virus (169), but such an explanation appears unlikely since the activation of herpes in pneumonia is extremely common

In Switzerland several reports have recently appeared indicating that the incidence of false positive serologic tests may be quite high in certain atypical forms of pneumonia, and even using such tests as a diagnostic criterion. Fanconi (82) suggested the term "Pseudo-luetic subacute hilifugal broncho-pneumonia" for the syndrome noted in four seropositive children with prolonged febrile pulmonary infection showing considerable infiltration in the region of the hilum by x-ray, seven additional cases were later reported (14) from the same pediatric clinic. In 1941 Hegglin (111, 112) reported 19 cases in adults of an atypical pneumonia with repeated strongly positive Wassermann, Kahn, and/or Citochol reactions which became negative within a few weeks. He suggested that these represented a new disease entity, "Wassermann positive pulmonary infiltration," since positive tests occurred uniformly in cases with this type of patchy, soft pulmonary infiltration, whereas in 680 cases of pneumonia and broncho-pneumonia without such infiltration only 2 8% had transient weak reactions to one or another test In the discussion of this paper Pulver added two similar cases. Benedikt (14) suggested that the above pediatric and adult cases might represent the same disease

Hegglin did not attempt to relate his cases to other types of pneumonia, although the descriptions appear to the reviewer to resemble closely "primary atypical pneumonia of unknown etiology" (Variety "X" or "Virus" pneumonia), which has been widely recognized only within the past five years There is no published evidence that false positive reactions are common in this disease. Kneeland and Smetana (167) mention "shifting Wassermann reactions" in their series of fifty-two cases, without data on their incidence, of nine cases presented in detail, only one atypical case, which was preceded by migratory arthritis, had a transient positive Wassermann test Drew et al (58) present one case with a doubtful Wassermann test, but do not mention positive or negative reactions in the rest of their fifty cases Many of the cases listed but not described in detail in the European papers may fall into this group, since the isolation of a pneumococcus was mentioned in none of them This problem may be clarified when etiological diagnosis of non-pneumococcal pneumonias becomes available, at present most cases are due to no known agent

In view of these European papers it seems surprising that there have been very few reports in America of biologic false positive reactions due to pneumonia (26, 167, 215, 281a) The incidence might be much higher if tests were performed later in the disease as well as on admission.

In two American reports of false positive reactions encountered in routine

pediatric cases (42, 120), as well as in several of the Scandinavian papers quoted above, it was emphasized that a large proportion of the reactions occurred in patients with mild infections In view, however, of the fact that a large proportion of cases visiting any pediatric or medical clinic suffer from respiratory infections, these results point to a very low incidence of false positive reactions in these common diseases

Mohr et al (215) reported positive tests in two cases of sore throat and one of labyrinthitis of unknown etiology Although the cases of sore throat did not have the hematological or immunological characteristics of infectious mononucleosis, it is known that the manifestations of this disease are very varied It seems likely that occasional atypical cases of infectious mononucleosis are misdiagnosed as the grip, sore throat, or common cold, especially since infectious mononucleosis was strangely absent from the Scandinavian collections of false positive cases

It is concluded that false positive serologic tests appear in an appreciable proportion of cases in some epidemics of atypical pneumonia, but it is questionable whether these form an etiologically separate group, as was suggested by Hegglin The incidence in other types of respiratory infection seems low, but may turn out to be high in certain strains of influenza, bronchitis, or other respiratory infections when an adequate etiological classification of these diseases becomes available Some of the reported cases of respiratory infection may have been undiagnosed infectious mononucleosis

(l) *Scarlet Fever* At the time when the Wassermann tests suffered from grave technical defects, scarlet fever crept into the literature as a frequent cause of false positive reactions There have been no confirmations of this concept in the past decade, other than five seropositive cases in one unconvincing report (255) Landau (186) recently tabulated the cases reported in twenty conflicting earlier papers He also performed Wassermann, Kahn, and Sachs-Georgi tests at two to four weeks after admission on 164 cases which were negative on admission Three of the cases were positive on only one occasion to one of the flocculation tests The sole case which was positive to all three tests and remained positive for several weeks was complicated by pneumonia of unstated etiology It therefore appears that scarlet fever is not a significant source of these reactions Indirect evidence in the same direction has been furnished by Lund, who found (personal communication) that a group of patients convalescing from scarlet fever had the same average level of "natural" Wassermann antibody (202) as the normal population

(m) *Disseminated Lupus Erythematosus* This disease, of unknown etiology, is included here among the infectious diseases because it is frequently febrile Coburn and Moore (43) recently reported thirty cases, of which 13 had a positive Kline test at some time, and 11 a positive or anticomplementary Wassermann reaction The reviewer had the opportunity to investigate one of these cases, an unquestionably false positive reaction in a child who was subsequently found at autopsy to have no pathological evidence of syphilis, her serum was positive in 1/2 or 1/4 dilution to the Kahn, Kline, Mazzini, Eagle, and Kolmer tests

(n) *Measles.* Pockels (247) reported that of convalescent sera from 206 children one to two weeks after the onset of measles, three were positive to both the Wassermann and Meinicke tests and eight positive or doubtful to one or the other test. In several the tests were repeatedly positive, but only a few patients were stated to have been retested a few months later and found negative Lane (194) reported eight strongly positive Kahn tests in 56 cases of measles in members of the Civilian Conservation Corps, who had had negative Wassermann tests on admission to the Corps These positive reactions appeared within the first three weeks of the disease, the five patients who were retested later were found to be negative Gunn (102) reported one strongly positive and 5 weakly positive Wassermann reactions in 53 convalescent sera obtained from measles patients but no clinical data were available to eliminate syphilis. One case of "pseudo-luetic bronchopneumonia" (82) followed an attack of measles It appears possible that the incidence of false positive reactions in measles is fairly high, although Eagle (69) noted no positive reactions in 13 cases It may seem surprising that this question should remain unsettled in such a widespread disease, but it may be because it is rarely hospitalized and tested The armed forces are in an excellent position to collect further data on this subject

(o) *Miscellaneous Infections.* Cases of *non-syphilitic venereal diseases* with false positive serologic tests are naturally subject to suspicion, since the presenting disease offers prima facie evidence for the possibility of having contracted syphilis Nevertheless, a high incidence has recently been reported in both *lymphogranuloma inguinale* (lymphopathia venereum) (37, 168) and *chancroid* (168) of positive reactions which were proved to be false by their rapid disappearance following treatment of the disease without anti-syphilitic therapy False positive reactions have been reported in occasional cases of lymphogranuloma (88, 153) and also *genital herpes* (169, 181, 212, 251) Another report on a variety of venereal diseases (264) is based on valueless arbitrary serologic criteria

In 25 *chicken-pox* convalescent sera Gunn (102) found 3 positive and 1 doubtful Wassermann tests, an even higher incidence than he found in measles, no further evidence is available on this condition. His 6 convalescent sera from *mumps* were all negative, but Smith (273) reports positive Sigma flocculation reactions in two young siblings, with seronegative parents, 6 weeks after the onset of this disease, one of these also had a weakly positive Wassermann reaction in the blood and the spinal fluid and died of mumps encephalitis The reviewer has seen a patient with mumps whose blood was positive to a number of serologic tests and then became negative within a few weeks

Typhus and *typhoid fevers* were frequently mentioned in the older literature, but the reviewer has been able to find only one reported case in the past decade of typhus fever with positive Wassermann tests (252) The irregularity of the reactions suggests imperfections in the laboratory in Indo-China which performed the tests In 64 cases of *Tularemia* (27) only one false doubtful Kahn test was found, from which it was concluded that this disease does not influence the specificity of the test

Subacute bacterial endocarditis was frequently mentioned in early reports as a

cause of biologic false positive reactions, but this has had no recent verification Wydrin's (310) series of 3 non-syphilitic cases without false positive reactions is too small to be of value *Weil's disease* was also reported in the past, possibly because of its spirochetal origin, but no reports have been found of such cases published within the last decade *Vincent's angina, diptheria, glanders,* and *rheumatic fever* fall into the same category *Infectious hepatitis* (catarrhal jaundice) has rarely been reported as a cause of false positive reactions (255), such cases are known to the reviewer and may not be too rare

Finally, we may mention the miscellaneous group of *fevers of unknown origin*—undiagnosed cases of prolonged fever and weight loss, often with hyperglobulinemia, occasionally with enlarged spleen, liver, or lymph nodes, which do not fit any recognized diagnosis and which occasionally have a positive serologic test for syphilis One such case was included in the series of Mohr et al (215), a similar case with chronic hemolytic anemia was reported by Kracke (179) Another was recently noted (249) in which the serologic diagnosis of syphilis led to arsenical treatment, which tragically resulted after two injections in an encephalitic reaction with permanent residual hemiplegia

(p) *Non-infectious Conditions—Hyperglobulinemia, Serum Inoculation, Miscellaneous* There appears to be a widespread but unwarranted impression that false positive serologic tests are often caused by any conditions which give rise to a marked *hyperglobulinemia* Hyperglobulinemia is in general caused by two types of disease 1) a variety of infections, in which at least part of the increased globulin is antibody, and 2) conditions not especially involving antibodies, such as cirrhosis of the liver, dehydration, and multiple myeloma There is no reliable evidence that any member of the second group is associated with these positive tests, it appears reasonable to regard the hyperglobulinemia and the occasional positive reactions of the first group as separate manifestations of the underlying infectious process, rather than to consider one the cause of the other In the Methods Evaluation Surveys (47, 240) large series of jaundiced sera have shown very few false positive reactions Although the emphasis was placed on the jaundice rather than abnormalities of the serum proteins, a large proportion of the sera were from cases of cirrhosis, in which the globulin is characteristically elevated and the albumin decreased Cardon and Atlas (36) have recently reported 8 cases (23%) of false positive reactions in 34 hyperproteinemic sera encountered in routine testing in the Cook County Hospital Their criterion of falseness was the presence of a positive Kahn but negative (in 2 cases anticomplementary rather than negative) Wassermann reaction, one case which was positive to both tests was automatically considered syphilitic This criterion is worthless In addition only 2 of their cases ever had a second test to eliminate the possibility of technical error A peculiar crystallized serum globulin from a patient with an undiagnosed arthritis was reported to give a positive Wassermann reaction (124), but this may well have been anticomplementary, like other isolated globulins (49)

Horse Serum injection was reported by Hentschel and Szego (119) to give rise to some degree of reaction to the Meinicke test in 81% of 51 serum-treated

diphtheria patients tested at intervals up to 3 weeks after inoculation. Only a small proportion gave weakly positive reactions to the Wassermann, Sachs-Georgi, or Kahn tests. Frei (87) confirmed the observation of frequent positive Meinicke tests in patients injected with horse serum, but he and Boas and Tolboll (23) found few or no positive Kahn and Wassermann reactions Frei pointed out that the Meinicke antigen, in contrast to the others, is derived from horse heart, which contains Forssmann antigen in common with the horse serum used for inoculation. Since all of the testing antigens in common use in America are derived from beef heart, which contains no Forssmann antigen, this cause of false positive reactions can probably be disregarded.

Menstruation, pregnancy, and various types of *malignancy* were often reported in the early literature as causes of false positive reactions but no evidence in support of this thesis was found in the Evaluation Surveys (47, 240) Similar results were obtained in other studies of sera taken during various phases of the menstrual cycle (127) and pregnancy (154)

Such diverse conditions as *diabetes, acetic acid poisoning, ether anesthesia, post-mortem* specimens, and treatment with various drugs were reported from time to time to give rise to false positive tests Such reactions are inconsistent with modern knowledge of antigen-antibody reactions, and have had no recent confirmation The latest member of this group is *sulfanilamide* (24, 254) which could not be confirmed in a series of cases studied by Rein (personal communication). Recent papers (6, 26, 78, 180) have included occasional transiently positive cases of a wide variety of diseases in which the incidence is so low as to be of little statistical significance or so high (278) as to be incredible

Positive reactions have been noted to develop rarely in *blood donors* after several donations (282a), the possibility of a causal relationship is under investigation.

5. False Positive Cerebrospinal Fluids

The number of spinal fluid specimens tested is very much less than the number of blood specimens, and reports of false positive spinal fluids are accordingly rare. Since high titers of Wassermann antibody circulate in the blood of patients with early syphilis without being detectable in the spinal fluid, and conversely, strongly positive spinal fluids may exist in CNS syphilis with only weakly positive blood tests, it follows that positive tests on spinal fluid ordinarily reflect the presence of an infectious process releasing antibody within the central nervous system Indirect evidence for the formation of antibody within the central nervous system in neurosyphilis was furnished by Kabat et al (139), who found a high proportion of gamma globulin in such spinal fluids, which could not be accounted for by filtration from the plasma In addition, Freund (89) has shown that rabbits passively immunized with typhoid antiserum develop only 1/300 as high a titer of antibody in the spinal fluid as in the serum, corresponding approximately to the ratio of total protein concentrations Morgan et al (223) have reported similar ratios in rabbits vaccinated against equine encephalomyelitis One would therefore not expect positive spinal fluid tests in the various

conditions discussed above as causes of false positive blood tests Two positive spinal fluids have been reported, however, in malaria (161, 305) and one weakly positive Wassermann test (273) in the spinal fluid of an infant who died of mumps encephalitis These reports must be viewed with suspicion, since spinal fluid tests are just as susceptible to technical error as are blood tests, and none of these was tested a second time

A number of cases have been reported in primarily neurological diseases Sezary and Terrasse (268) in 1935 reviewed the 25 cases of positive spinal fluids in cases of central nervous system tumors reported in 14 earlier papers, and added 4 cases with negative blood tests Two of these cases had a negative spinal fluid when retested McLean and Munger (211) reported 10 presumably false positive spinal fluids in a variety of neurological conditions—encephalomalacia, streptococcus septicemia, electrical burn, cerebrospinal rhinorrhea, concussion, skull fraction, neuritis, and multiple sclerosis Most of these were negative when repeated, the only two cases which had two positive spinal fluids were cases of encephalomalacia A positive spinal fluid with negative blood tests was reported in single cases of post-traumatic convulsions (133), pneumonia and meningitis (258), meningococcus meningitis (26), and encephalitis (220), the first two patients were retested and found negative The reviewer has seen a patient in the Neurological Institute with positive Wassermann tests on 4 spinal fluids drawn several months following the onset of meningococcus meningitis, the blood was negative and the history offered no basis for suspecting syphilis

It is the opinion of the reviewer that many of the above reactions, which were not retested or were negative when retested, were probably due to technical error There exists no clear evidence today for the production of biologic false positive spinal fluid tests for syphilis in various systemic or central nervous diseases It is hoped that further reports on this subject will be better documented, with tests in more than one laboratory and on more than one specimen from the patient [3]

III LABORATORY DIFFERENTIATION OF FALSE POSITIVE SERA

1 *The Mechanism of the True Serologic Tests for Syphilis*

Because the antigens used in the Wassermann and flocculation tests are derived from sources (mammalian tissues) which are biologically distant from the infectious organism, the reaction was long considered not a specific antigen-antibody reaction but rather the result of mysterious colloidal alteration of the serum proteins (e g , 206, 293) The substance reacting in the serum was therefore termed a "reagin" rather than an antibody This conception was reinforced by the observation that the addition to the antigen of cholesterol, which also bears no apparent relationship to the organism, increased the sensitivity of the reaction It has been adequately demonstrated, however, especially by Eagle, that the flocculation and Wassermann reactions have all the essential

[3] Scott et al (267a) have recently reported several repeatedly positive spinal fluids occurring in cases of meningococcal, tuberculous, and aseptic lymphocytic meningitis This reaffirms the danger involved in diagnosing syphilis on serologic grounds alone

characteristics of specific agglutination (62) and complement fixation (63) tests [4] The role of cholesterol was shown to be that of enlarging the particles of water-insoluble lipid antigen and thereby increasing their effective surface (64), a similar effect was produced by a wide variety of alcohol-soluble, water-insoluble substances ranging from ergosterol to collodion (65) That the action of cholesterol may not be entirely passive has been suggested by the observation of Wadsworth, Maltaner, and Maltaner (291) that cholesterol was somewhat anticomplementary and reacted with some normal sera in complement fixation tests Lund (personal communication) has recently noted that cholesterol may adsorb the small amounts of presumably natural Wassermann antibody which he has found in normal sera (202)

The various tests are usually reported as 1 to 4 plus reactions, which give an impression of being more quantitative than they really are When quantitatively tested by serial dilutions, the serum of a patient with florid early syphilis usually shows a 4 plus reaction (complete flocculation, or complete inhibition of hemolysis in the complement fixation reaction) in dilutions of 1/16 to 1/64, and may occasionally reach a titer of 1/512 A 4 plus reaction as ordinarily reported on undiluted serum therefore does not distinguish low titer from high titer sera, while the 1 to 3 plus (partial) reactions represent only a very narrow range of low antibody concentration

Estimation of antibody concentration by serial dilution to the endpoint of flocculation or complement fixation is only roughly quantitative, for other factors play a secondary role in the reaction and may swing the balance of a weak reaction to positive or negative. The most important of these are variations in the sensitivity of the antigen, to be discussed below, and in the mechanics of test performance In addition, an inhibitory factor appears to be present in some sera since the reviewer has observed electrophoretically isolated globulin fractions, and Nishio (229) has noted chemically separated fractions, which had a higher flocculation titer than the original sera, although their antibody content could have been no higher than that of the sera A further source of error in complement fixaion tests is the tendency of certain sera to be anticomplementary —i.e , the control tube containing serum without antigen "fixes" complement, preventing detection of specific complement fixation by antigen plus serum The Wassermann antigens of an earlier day were frequently moderately anticomplementary, so that the summation of a subliminal anticomplementary effect of serum plus a similar effect of antigen could produce an apparent positive reaction with a negative control tube (68) With good Wassermann antigens the danger of technical false positive reactions from this source is now slight.

It has been stated (71) that the incidence of anticomplementary reactions is

[4] In this review the antigens used in the serologic tests for syphilis are grouped under the term "Wassermann antigen," and the substances in syphilitic or false positive sera which react with this antigen are referred to as "Wassermann antibody" (Cf 301) This term is considered preferable to "syphilitic antibody," for it is likely that syphilis produces other antibodies in addition to this one It is particularly recommended that the term "reagin" be abandoned in this connection since it is used with another meaning in the field of allergy

more frequent in syphilitic than in non-syphilitic sera Such reactions, however, cannot serve as a basis for suspecting syphilis, for pure normal gamma globulin is regularly highly anticomplementary (49) and anticomplementary reactions are particularly frequent in diseases (cirrhosis of the liver (95), lymphogranuloma inguinale (103), multiple myeloma (103, 132), lupus erythematosus (43), in which the gamma globulin is markedly increased

Other factors which introduce irregularities in the serologic tests are (a) the zone reactions of certain sera, of which only higher dilutions may react in flocculation or complement fixation tests, and (b) the necessity of "inactivating" sera by heating for 30 minutes at 55–57 C before testing This procedure was originally introduced to destroy the native complement of the serum, in order to prevent it from varying the amount of complement present in the fixation test It was subsequently found that the heating eliminated the undesirable anticomplementary action of most of those sera which were anticomplementary in the fresh state, and when the flocculation tests were introduced it was found that most positive sera were less active or entirely inactive unless heated before testing Whether this inhibition of flocculation by unheated serum depends on complement or some other thermolabile component is not clear, it does not depend on changes in the antibody since purified Wassermann antibody prepared from unheated serum is equally active with or without previous heating (50) Sera have been noted (164) in which the flocculation reaction was stronger *before* heating, but this is distinctly the exception It has also been observed (259) that the inhibitory effect of unheated serum is abolished by hypertonic saline, which has been the basis of certain tests in which heating of the serum is eliminated

All the above complications may be of importance in only the rare, unusual case In spite of all the imperfections which these tests share with other serologic procedures, and in spite of the fact that the antigens employed are not derived from the infectious agent, the fact remains that the serologic tests for syphilis, when properly performed, are surprisingly good rather than discouragingly bad Certainly no serologic test for any other disease has ever been applied on nearly so large a scale as the Wassermann and related tests In general, serologic tests for other diseases, which employ the organism as antigen, are used only when there is some clinical indication The difficulty with the serologic test for syphilis is that the nature of the disease, with its latent stage concealing potential serious illness, forces us to place an excessive burden on a laboratory procedure which cannot be expected to be infallible

2 *Possible Mechanisms of the False Positive Tests*

Biologic false positive serologic tests for syphilis may conceivably be caused by the presence in serum of (a) an antibody identical with the Wassermann antibody produced in syphilis, (b) an antibody differing in some ways from the true Wassermann antibody, but cross-reacting with Wassermann antigen or some component thereof, or (c) physico chemical changes, not involving antibodies, which produce flocculation or complement fixation reactions

Consideration of the first possibility involves the mechanism of production of the Wassermann antibody in syphilis, which will be discussed in detail later If the antibody is formed in response to Wassermann antigen released from the host's tissues in a suitable form, rather than to spirochetal antigen, it would not be surprising if other disease agents occasionally produced the same reaction. In such cases the antibodies would be identical and no possible improvement in the serologic tests for Wassermann antibody could eliminate false positive reactions There is no way of knowing at present what proportion, if any, of non-syphilitic positive tests belong to this category

If there is hope for solution of this problem it rests on the assumption that false positive sera fall into the second category—that of cross-reacting but not identical antibodies, which may ultimately be distinguished from Wassermann antibody by chemical or immunological phenomena. Several examples of heterophile, cross-reacting antibodies which may sometimes be distinguished by absorption experiments have been reviewed by Buchbinder (30) An excellent example is the production of sheep cell agglutinins in man as a result of infectious mononucleosis or horse serum inoculation. Although indistinguishable in their reaction with sheep cells, these two antibodies differ in their absorbability by guinea pig kidney or by the red cells of various species (279)

The third concept derives from the day when the serologic tests were considered labile colloidal phenomena Nevertheless the possibility cannot be excluded that certain false positive reactions may be less specific in their character than the true tests The cephalin flocculation test (105) for liver function, in which a cholesterolized saline emulsion of a lipid is flocculated by certain sera, bears considerable superficial resemblance to the flocculation tests for syphilis, although physicochemical studies have failed to elucidate its mechanism (137), there is no basis for suspecting that it involves an antibody It appears, however, more profitable to seek differences between the substances causing the reactions of true and false positive sera than to debate whether these substances are antibodies. Flocculation of Wassermann antigen by high concentrations of divalent cations (245) or by hypotonic saline (59) is not applicable to the problem since the concentration of electrolytes in sera varies within limits which are too narrow to permit an appreciable effect upon the test Kolmer (173a) still favors the view that the substance causing false positive reactions is not an antibody

It has been suggested that the transient positive serologic tests which are caused by diseases other than syphilis may not be false, but may represent stimulation by the so-called "anamnestic" reaction of increased production of Wassermann antibody in cases of syphilis in which this antibody is present in concentrations below those required for a positive diagnostic test This hypothesis, for which there is no direct evidence, is contradicted by the failure of Eller (79) to obtain a higher incidence of positive serologic tests after inoculation of malaria in 22 seronegative treated syphilitic than in a series of non-syphilitic patients Furthermore, Heidelberger and Kendall (115) and Kabat and Heidelberger (138) were unable to demonstrate the anamnestic reaction in a few rabbits by means of accurate quantitative chemical measurements of antibody to egg albumin or

serum albumin Since the concept of the anamnestic reaction is based solely on data secured with unreliable quantitative titration methods, it appears questionable whether the phenomenon exists at all

3 *The Nature of the Wassermann Antigen*

Since the Wassermann antigen and related alcohol-soluble antigens have recently been reviewed in detail by Weil (301), the subject will be discussed only briefly

(a) *Serodiagnostic Antigens, Discrepancies in Response to Various Tests* The various antigens used in the common serologic tests for syphilis consist essentially of an alcoholic extract of dried beef heart, the sensitivity of which is increased by the addition of cholesterol or some other sterol (While other mammalian tissues contain the antigen, beef heart has proved to be the best source) Moderate purification is effected by preliminary ether extraction of the beef heart and in some cases precipitation of the antigen by acetone, but the final products contain a great deal of contaminating material which may well participate in some of the false positive reactions As was indicated in an earlier section, it is possible by altering the concentration of various constituents to alter the sensitivity of these antigens [5] A few years ago Eagle (71) emphasized the view that differences in response of a serum to various tests were dependent on the sensitivity of these tests Further experience, however, in laboratories performing a variety of tests of carefully standardized sensitivity, has shown that sera of some syphilitic patients will react consistently with certain tests and other sera only with other tests A few examples of such anomalous patterns are shown in Table II, furnished by the Venereal Disease Research Laboratory of the U S Public Health Service

This matter is of some practical importance since patients suspected of having false positive reactions are often subjected to repeated tests by a variety of procedures, and the failure to secure uniformly positive results with all tests is sometimes considered a "peculiar," probably false positive, reaction This view is unwarranted, for while most strongly positive sera are positive to all tests, this irregular behavior is characteristic of some syphilitic as well as nonsyphilitic weakly positive sera The probable reason that the phenomenon has been less frequently observed with known syphilitic sera is that patients with clinical evidence of the disease are not usually subjected to numerous repeated tests Another factor contributing to the irregular behavior of weakly positive sera is the inevitable day-to-day fluctuation in the sensitivity of the tests This was shown by the Evaluation Surveys (47, 240) and by Mohr and Smith (216), who found that the marked daily fluctuation in the Eagle complement fixation reactions of a group of weakly positive syphilitic patients were eliminated when

[5] "Screen Tests" for the rapid exclusion of syphilitic reactions in sera have been developed by the deliberate increase in sensitivity of certain antigens (e g , Kahn Presumptive, Kline Exclusion) to the point where some specificity is sacrificed Since these antigens are used only to indicate the need for further tests with standard serodiagnostic antigens on the positive specimens, they are not a source of false diagnoses and will not be be considered here

TABLE II

Serologic Tests of Cases of Primary Syphilis under Treatment

DATE	KAHN STANDARD	KOLMER COMP FIX	EAGLE MACRO	HINTON	MAZZINI
			Case 1		
4–13–42	4	N	P 64	P	4
4–20–42	4	N	P 8	P	4
4–27–42	4	N	P 8	P	4
5– 4–42	4	N	P 2	P	4
5–11–42	3	N	P	P	4
5–18–42	1	N	P 1	P	4
6– 1–42	N	N	N	P	1
			Case 2		
8–25–42	4	4	P 8	P	4
9– 2–42	3	4	P 2	P	3
9– 9–42	3	4	P 2	P	3
9–16–42	2	4	D	P	3
9–23–42	N	±	N	P	3
9–30–42	N	N	N	D	1
10– 7–42	N	N	N	N	1
10–14–42	N	N	N	N	1
			Case 3		
9–16–42	4	4	P 8	P	4
9–23–42	4	4	P 2	P	4
9–30–42	3	4	P 1	P	4
10– 7–42	3	4	N	D	4
10–14–42	1	4	N	N	4
10–21–42	1	4	N	N	4
10–28–42	N	4	N	N	4
11– 4–42	N	4	N	N	4
			Case 4		
3–23–42	4	4	D	P	
3–30–42	2	4	N	P	
4–15–42	N	4	N	N	N
4–20–42	N	4	N	N	N
4–27–42	N	4	N	N	N
5– 4–42	N	4	N	N	N
5–11–42	N	N	N	N	N

Results are reported as negative to 4 plus except in the Eagle and Hinton tests which are reported as P (positive), D (doubtful), or N (negative) Positive Eagle tests are also reported in titered units—the numbers denote the highest dilution giving a positive test The other tests were not titered

It will be noted that Case 1 had a negative Kolmer test even when all the others were positive and the Eagle test had a titer of 64, in case 3 the Kolmer and Mazzini tests remained positive long after the others, while in case 4 the Kolmer alone persisted as positive.

these sera were frozen and then tested simultaneously at the end of the experimental period

The mechanism of the specificity of certain tests for certain sera is not clear Brown (28) has presented evidence that substances inhibiting flocculation exist in certain sera Another factor may be variation of the different antigens in their content of minor antigenic components which do not ordinarily play an important role in the reaction

(b) *Purification of Wassermann Antigen* Purification and chemical identification of the active component of the antigen would obviously be an important step in further improvement and standardization of the tests A great deal of work in this direction has thus far yielded incomplete chemical information since the cosolubility of mixed lipids makes their purification extremely difficult The solubility in alcohol and ether and insolubility in acetone, which formerly caused the antigen to be considered a lecithin, is no proof that it has the structure of this group of compounds The furthest advance in purification appears to be that of Pangborn (234, 235), who has separated from the nitrogen-containing lecithins of beef heart a non-nitrogenous phosphorus-containing lipid which she named "cardiolipin" and considered to be a new type of phospholipid containing a polysaccharide phosphoric acid esterified with fatty acids In view of the difficulty in separating mixed lipids, however, the constancy of phosphorus content and serologic activity on several reprecipitations by no means proved that the material is a pure compound This material was reported curiously to be anticomplementary by itself but to be an effective complement-fixing antigen when mixed with lecithin and cholesterol, which separately are serologically inert A mixture containing 0 03% cardiolipin, 0 05% lecithin, and 0 4% cholesterol was stated to be as active as the ordinary Wassermann antigen used in the New York State Laboratories Its use in flocculation tests has also been reported (28) It will be of great interest to see how such purified material, when available in larger quantities, reacts with false positive sera and with sera which show a selective response to various tests

(c) *Antigenicity of Wasserman Antigen* One obstacle to the earlier acceptance of the Wassermann antigen as a true antigen was its failure to produce antibodies on injection into animals This was clarified by the discovery by Landsteiner that certain relatively simple chemical substances (haptens), which react in vitro with a specific antibody but cannot induce its formation in vivo, will do so when mixed with a foreign protein as "Schlepper" The demonstration of this phenomenon with the alcohol-soluble Forssman antigen mixed with pig serum (191) was soon followed by the similar experiments of Sachs, Klopstock, and Weil with Wassermann antigen (261, confirmed in 195), as well as by the demonstration of the antigenicity of Wassermann antigen when flocculated with syphilitic serum (67) Although the Wassermann antigen appears to be almost universally distributed in mammalian tissues, it is not generally available in effective antigenic form without treatment of the tissue, as is emphasized by Weil (301) Furth and Kabat (90) have shown that the Wassermann antigen is saline extracts

of tissues is bound to heavy particles which are readily sedimented in moderate ultracentrifugal fields (27,000 r p m. for 1 hour) These particles reacted in vitro as a Wassermann antigen, but failed in the doses used to provoke a positive Wassermann reaction when injected into rabbits An exception to this non-antigenic behavior of mammalian tissue has been reported (126)

(d) *Spirochetal versus Autogenous Origin of the Antigen.* The presence of Wassermann antigen in the tissues of the host has given rise to the still unresolved conflict over the origin of the Wassermann reaction—whether in response to antigen released from the host's tissues or from the spirochetes The early suggestion by Weil and Braun (302) of an autogenous origin was overruled by the objection that such a reaction might be expected in all diseases involving tissue destruction Following the discovery of the hapten phenomenon Sachs, Klopstock, and Weil (261) in 1925 rejuvenated this doctrine by the suggestion that autogenous lipid antigen was activated by combination with a particularly suitable "Schlepper" protein furnished by the spirochete. This concept, which is characterized by ingenuity but not by direct experimental evidence, retains a sympathetic consideration in the recent review of Weil (301) It has, however, been opposed by Landsteiner and Van der Scheer (192, 193) on the basis of the demonstration of the production of Wassermann antibody in rabbits in response to dead trypanosomes of a strain producing such reactions in infections, and by Eagle (71a) on the basis of numerous demonstrations (12, 73, 122, 123, 166, 184) of such an antibody response to inoculation of killed spirochetes of non-virulent strains Objection may be raised to the experiments with spirochetes since it has not been possible to cultivate even non-virulent spirochetes on media free of animal tissue, and hence any antigen present in the washed organisms might have been derived from the medium It is hoped that improvements in synthetic media will eventually clarify this problem.

To the reviewer the most impressive evidence for the existence of Wassermann antigen in the organisms causing such reactions is that of Landsteiner and Van der Scheer (192, 193), who obtained the antigen (trypanosomes) from rat blood, which in adequate control experiments led to no formation of Wassermann antibody. It may, however, be argued that even if the antigen is present within the trypanosomes rather than as a surface contaminant, organisms growing in a mammalian host may have derived their Wassermann antigen from the host's tissues, for similar phenomena have been found in vitro Olitzki and Bernstein in 1916 (232) demonstrated that inoculation of bacteria cultivated in media containing human ascitic fluid led to formation of antibodies to this fluid. Failure to remove the contamination by thorough washing was taken to indicate incorporation of the foreign antigen within the organism More recent demonstrations of the addition to bacteria of animal proteins (4) or the ordinarily non-antigenic agar (274, 275) have shown that the phenomenon is rather one of adsorption, since it has been shown to occur with collodion and other non-living particles (4, 134) and with non-growing bacteria in the cold (311) Consideration of such reports has led Kabat (136, p 554) to lean toward the autogenous theory of the origin of Wassermann antibody.

It is not entirely an academic question whether the organism absorbs or adsorbs the entire antigen molecule, or synthesizes it from simpler materials which are ultimately derived from the host Such bacterial synthesis might lead to the expectation of variation in the structure of the antigen and hence in the nature of the antibody, while if various organisms are capable of some degree of rendering active the host's own Wassermann antigen, the "false positive" antibodies thus formed might be expected to be indistinguishable from the syphilitic ones The autogenous origin of the antigen would also offer a ready basis for explaining the development of false positive reactions In view of the ubiquitous occurrence of this antigen, however, it is also easy to conceive of this or related antigens as existing in low concentration in a variety of infectious agents which only occasionally give rise to positive reactions

There are no critical data by which to decide between the autogenous and spirochetal theories The vast body of evidence for the formation of various antibodies in response to the antigens of infectious agents appears to the reviewer to place the burden of proof on those who would postulate a fundamentally different mechanism in the formation of the Wassermann antibody The recent study of certain virus infections and tumors has given rise to several new examples of the same problem—cold autohemagglutinins formed in response to atypical pneumonia of unknown etiology (244, 288), antibodies to normal mouse and human lung appearing during certain respiratory infections (285), and a natural antibody in adult rabbits, independent of Wassermann antibody, which fixes complement with a variety of tissue extracts (159) [6] Kabat (136) has suggested that all of these may have arisen from activation of tissue antigens With regard to detecting false positive serologic tests for syphilis, however, it seems of less moment to decide whether spirochetes contain Wassermann antigen than whether they contain other antigens which might be used as the basis of a diagnostic test

With regard to the possibility of Wassermann antigen existing in those organisms which cause false positive reactions, it may be noted that Ishibashi (129) produced positive Wassermann reactions in 2 rabbits immunized with ether extracts of leprosy bacilli mixed with swine serum as "Schlepper," 2 rabbits immunized with whole organisms failed to develop the reaction These experiments were reported in insufficient detail and on too few animals

4 *Spirochetal Antigens*

(a) *Earlier Studies* Shortly after the discovery of the Wassermann reaction and of the spirochete of syphilis Noguchi (230) reported the cultivation of the organism, and he and others (44, 178, 230) reported the use of such cultivated organisms in a specific complement fixation test for syphilis Neither this nor any other claim of the retention of virulence by cultivated so called *Treponema*

[6] The material in normal animal sera which flocculates various tissue extracts, claimed by Duran-Reynals (61) not to be an antibody, appears from his own data to be very likely the natural Wassermann antibody of animal sera, to be discussed below In interpreting these results he neglected to consider that serum contains many antigens

pallidum has survived, and it is universally accepted that the several strains represent either saprophytic contaminants of the original chancres or else attenuated true *Treponema pallidum* which has lost its virulence for rabbits in becoming adapted to an artificial culture medium Nevertheless, though these cultivated organisms are biologically, and hence immunologically, not identical with the organisms causing syphilis in man, subsequent work on their use as antigens has provided encouraging evidence of their reaction with syphilitic sera

(b) *Independence of Wassermann and Spirochetal Antigens* Although cultured spirochetes have been subjected to alcoholic extraction (12, 122, 166, 184, 253, 292) with varying degrees of success in an effort to obtain a more specific Wassermann antigen, the main promise of spirochetal antigens appears to the reviewer to lie in the opposite direction, since false positive sera which react with the lipid antigen of the spirochete (or tissue) may well lack antibodies to *other* antigenic components of the spirochete. Many species of bacteria have been found to possess a high degree of antigenic complexity, including proteins, lipids and carbohydrates, which may be expected to be shared by the *Treponema pallidum.*

A number of investigators have provided evidence of antigenic differences between spirochetes and Wassermann antigen Although Hoeltzer (123) found in inadequate experiments that cultured spirochetes absorbed the Wassermann antibody from human syphilitic sera, Kroo (184) obtained opposite results Gaehtgens (91) noted that "Palligen" (described below) produced in rabbits a high titer of antibodies to itself and a low titer to Wassermann antigen, in contrast to the approximately equal titers found in syphilitic rabbits, suggesting the presence of other antigenic components in this spirochetal antigen Eagle and Hogan (73) observed no effect of exhaustive absorption with Wassermann antigen on the reaction of human syphilitic sera with Palligen. Although they did find that Palligen, on the other hand, absorbed the antibody of the Wassermann reaction, they have since been unable (personal communication) to repeat this observation with freshly cultured Reiter strain spirochetes This suggests that the proprietary Palligen may have contained beef-heart lipid, although it is also possible, inasmuch as Eagle observed a large proportion of amorphous debris and soluble antigen (73, 80) in Palligen, that the material during the period of transportation from Germany had released lipid antigen ordinarily bound within the organisms. Beck (12) and Kolmer et al (176) similarly observed independent absorption from human syphilitic sera of the antibodies to Wassermann antigen and to various strains of spirochetes, and concluded (12, 172) that the two types of antibody are distinct

In summary, while there may yet be some question as to the presence of Wassermann antigen in cultured spirochetes or in *Treponema pallidum*, there can be no question that all of these organisms have important antigens entirely distinct from Wassermann antigen. This antigenic independence may permit a spirochetal antigen of even imperfect specificity to furnish a useful verification test for sera positive to the usual lipid antigens

(c) *"Palligen" Complement Fixation Antigen* The most encouraging reports on a spirochetal antigen have been those concerned with "Palligen," a proprietary preparation of phenolized cultured Reiter strain spirochetes introduced in Germany in 1929 by Gaehtgens (91, 92, 93) Since this was patented and commercially produced, its mode of preparation was never published The following decade produced 20 papers in German literature (for bibliography see 80, 94) attesting to its superiority in sensitivity and specificity to the Wassermann antigen derived from beef heart Nevertheless, the notorious variability of the performance of the tests with which it was compared justifies cautious acceptance of such conclusions

The results obtained with limited use of Palligen in this country have been moderately promising Erickson and Eagle (80) found it more sensitive than the Eagle complement fixation and flocculation tests and apparently highly specific, since syphilis was subsequently proved in 14 of the 17 cases in 542 routine hospital admissions which had a positive Palligen but negative Eagle test In leprous sera both Eagle et al (74) and Patrick and Wolfe (242) reported a lower incidence of positive reactions with Palligen than with the usual serologic tests In malaria, however, Eagle et al (75) reported an even greater incidence of reactions with his own preparation of Reiter and Kazan strain spirochetes than with Wassermann antigen, as had Heinemann (118) in Germany with Palligen Erickson and Eagle (80) emphasized the danger of relying on Palligen for routine testing since the dilution used in the test is excessively close to the anticomplementary dilution, but Eagle stated (75) that his own preparation of spirochetal antigen had a much wider margin of safety between the anticomplementary and the reactive dilutions

(d) *Other Cultured Spirochetal Antigens* In spite of this promising background, work with spirochetal antigens in this country received a discouraging setback in the 1941 Evaluation Survey (240, 173) Palligen was not tested in this survey, but Eagle's spirochetal antigen gave 1 9% and Kolmer's preparation of the Reiter strain 6 3% false positive reactions in non-syphilitic cases excluding malaria and leprosy—values distinctly beyond the limits tolerated for Wassermann antigens in the same survey In sensitivity the Eagle spirochetal antigen rated 75 9% as opposed to 59 2% for his Wassermann antigen, while Kolmer's spirochetal and Wassermann antigens showed 70 6 and 74 1% respectively The disappointing lack of specificity extended even somewhat to leprosy, in contrast to the earlier findings, since the two spirochetal preparations were not significantly more specific than certain other complement fixation or flocculation tests

Kolmer et al (175, 176, 177) have published unsatisfactory results of testing various strains of spirochetes with syphilitic and non-syphilitic sera Although all the strains were as sensitive as the Wassermann antigen, false positive reactions ranged from 13 5% with the Reiter strain and 22 9% with the Nichols-Hough strain to 79 4% with a strain of mouth spirochetes Since the highest incidence of such reactions occurred with mouth spirochetes, Kolmer concluded that "antigens of the Reiter and other alleged cultures of *S pallida* cannot be used with any advantage in the serum diagnosis of syphilis," probably because

of the frequency of cross-reactions in normal subjects with antibodies to the common mouth spirochetes To the reviewer the data of Kolmer, which differ strikingly from the experience of other investigators, fail to justify such a sweeping condemnation of spirochetal antigens and can properly be applied only to his own preparations

Beck (12) has similarly found considerable antigenic variation in the available strains of cultivated spirochetes By cross-reaction and cross-absorption experiments with rabbit antisera, he found that the Reiter and Kazan strains were practically identical, as had been noted earlier in Kazan, USSR (123), whereas the Kioo and Noguchi and a mouth strain were practically completely independent of each other The spirochetal antigens were more sensitive than the Wassermann antigen in testing several hundred syphilitic sera, the Reiter and Kazan strains were best, and even the mouth strain reacted with 59 2% of the sera In specificity, the Reiter strain produced only 0 4, the Kazan 1 8, and the mouth strain 4 4% of false positive reactions Even though these strains are relatively independent antigenically, it appears that syphilis produces antibodies which react to some degree with all of them The high degree of specificity should encourage further work on cultured spirochetes, aimed at isolation of even more specifically reacting strains than those at present available, and of antigen fractions other than Wassermann antigen

(e) *Antigens of True Preponema Pallidum* As has been emphasized by Eagle (77, 71a), the solution of the false positive problem will probably appear when true *T. pallidum* is available for use as an antigen Thus far all attempts to cultivate this organism have failed, possibly the newer knowledge of the nutritional requirements of microorganisms will lead to renewed attack on this problem The methods of growth in chick embryos (277) or tissue cultures (155, 304) have not been successful

The only source of true *T. pallidum* at present is infected animal tissue. Noguchi's (230) suspension of testicular syphilomas of rabbits was not freed to any degree of host tissue An attempt to obtain relatively pure suspensions of "tissue" (virulent) spirochetes from this source was first reported by Hoeltzer and Popoff (122) Kolmer (177) has recently reported better results with such material than with cultured spirochetes, while Eagle and Hogan (73) have stated that technical difficulties have so far prevented the preparation of suspensions sufficiently free from tissue extractives and sufficiently concentrated to be useful Although such material could never be expected to be produced in quantities large enough for widespread testing, pressing need for a verification test in the occasional perplexing case warrants further work along these lines

(f) *Agglutination Tests* Although complement fixation tests with cultured spirochetes appear promising, agglutination tests with the same organisms have invariably yielded a high proportion of reactions with normal sera (12, 34, 73, 176) Kolmer (177) reported encouraging results with tissue spirochetes with a very small series of 6 sera

(g) *Chemical Composition.* In connection with the production in syphilis of antibodies to a lipid antigen, it may be noted that trypanosomes, of which cer-

tain strains have been found to produce positive serologic tests for syphilis (183, 189), have been reported to have an exceptionally high (40-60%) content of lipid (162, 163) So far as could be ascertained no studies on the gross chemical position of spirochetes are available

5 The Nature of Syphilitic Antibodies

(a) *Wassermann Antibody in Positive Human Sera* There is adequate evidence that the Wassermann antibody, like all other antibodies, is a modified globulin It would not be profitable to review the earlier disputes as to whether it was a euglobulin or a pseudo globulin since neither the methods of fractionation nor the methods of serologic testing were well standardized In almost all of these studies the serologic tests were confined to complement fixation, which are unreliable with globulin fractions because of their anticomplementary tendency (49) As was pointed out by Eagle (68), numerous earlier claims of artificial production of positive Wassermann reactions by various types of chemical and physical treatment of normal sera could best be explained as a summation of the subliminal anticomplementary effect of the earlier antigens with the anticomplementary effect induced by these modes of treatment It has recently been stated (1, 271) that normal sera contained with certain strains of B subtilis develop a positive Wassermann test without being anticomplementary, this remains to be confirmed

Eagle (70) has measured the amount of nitrogen precipitated by antigen from syphilitic sera of known titer and shown that a positive flocculation test was produced by 0 3 mg of antibody protein per 100 ml of serum, which is approximately 1/20,000th of the total protein present Thus the Wassermann antibody of even a syphilitic serum of high titer (e g 1 64) would represent only a fraction of 1% of its protein Witebsky (306, 307, 308) recovered purified Wassermann antibody from specific floccules by heating, a method introduced for other antibodies by Landsteiner and Jagić (188), while Bier and Trapp (20) used Heidelberger and Kendall's (116) method of dissociation by 15% NaCl The small amounts of antibody recovered in these investigations were not further studied Kolmer (171) failed to obtain a solution of pure antibody by the treatment of floccules with organic solvents Methods using either 15% NaCl plus ether or alcohol plus ether have recently yielded from large volumes of high-titer sera sufficient Wassermann antibody for physicochemical study (50) Serologic testing of electrophoretically separated fractions, as well as electrophoresis of purified antibody, showed that the antibody had a mobility intermediate between beta and gamma globulin (50), as had been demonstrated for a number of antibodies in animal sera, although most antibodies have the mobility of gamma globulin (Rev in 136) The fact that no separate component could be seen at that position in the electrophoresis of syphilitic serum was consistent with the extremely low concentration of this antibody

Ultracentrifugation of whole serum was shown by Deutsch (55) to result in relative concentration of the antibody in the sediment, indicating that the antibody was a heavier molecule than the bulk of the serum globulin, by calculations

of very limited reliability she concluded that it had a molecular weight of 1,130,000 While Davis et al (50) were able to confirm the relative concentration of antibody in the ultracentrifuged sediment of syphilitic sera, their preparations of purified antibody showed both a light component and a heavy component, of sedimentation constants 7 and 19 Svedbergs, corresponding to the globulins of molecular weight 160,000 and 990,000 which had been observed in numerous animal antisera The only other purified human antibody to have been studied in the ultracentrifuge was from a convalescent pneumonia patient and had a molecular weight of 160,000 (135)

The earlier observation of Hartley (106) that removal of the alcohol and ether soluble constituents abolished the Wassermann reaction of syphilitic sera, as well as some (but not all) precipitin reactions of various rabbit antisera, has been confirmed by Horsfall and Goodner (125) for certain types of antisera This observation of Hartley is difficult to reconcile with the serologic activity of purified Wassermann antibody which had been treated with these reagents in the process of preparation (50)

(b) *Natural Wassermann Antibody in Normal Human Sera* Purported demonstrations of the existence of small amounts of Wassermann antibody in normal sera have been based on ultramicroscopic examination of the floccules (209), addition of the normal serum to subliminal amounts of syphilitic serum or globulin (7, 267), a "widespread Kahn" test in which the ratio of serum to antigen is increased (269, 270), and alteration of the antigen so that it is precipitated by almost 100% of normal sera (145, 151) These studies fail to prove their point since they neglect the facts that an altered antigen does not necessarily interact with the same substance as the original antigen, and that variations in the concentration of antigen and of serum proteins have an appreciable effect on flocculation Thus the flocculation or complement fixation titer of purified Wassermann antibody was found to be increased 2 to 4 times by the addition of normal serum or albumin (50)

Lund (202), however, has succeeded in demonstrating the presence in normal serum of Wassermann antibody, using the technic of exposing Kline antigen to larger volumes of serum than usual, centrifuging, and resuspending the floccules in a small volume The incidence of such reactions increases with increasing ratios of serum to antigen, the majority of normal subjects showing positive reactions with ratios 10 times those used in the diagnostic test The presence in non-syphilitics of small amounts of Wassermann antibody is no more surprising than the presence in normal sera of low titer antibodies to a variety of organisms and red cells. While the origin of these natural antibodies is still a matter of dispute (187), the potential practical significance of this fact is that false positive tests in healthy individuals may represent a concentration of this natural antibody which exceeds the threshold of the diagnostic test Any differences which exist between the low titer natural antibodies and those of syphilitic sera might therefore be expected to apply to this class of false positive sera Work in this direction is being pursued by Lund (personal communication) A basis for the supposition that such differences might exist is offered by the observation by

Landsteiner and Reich (190) in 1907 of differences between natural and induced hemagglutinins in adsorbability by casein, stability to heating, and degree of cross-reaction with the erythocytes of various species Unfortunately the difference in degree of cross-reaction, which is less empirical than the other observations, was not as striking as might be desired

(c) *Wassermann Antibody in Animal Sera* Positive flocculation and complement fixation tests for syphilis have been reported in a high proportion of normal rabbits, mice, horses, cattle, and many other species of animals, Kemp et al (158) have recently reviewed 90 references which deal with this subject The significance of these observations seems to be simply that the natural antibodies occur at higher concentration in these species than in man The reviewer agrees with Kemp that " the frequency with which positive tests for syphilis occurs in animals other than man is not relevant to the problem as to their validity in man " The occurrence of this natural antibody in rabbits is a source of error in experimental work done with these animals

(d) *Other Syphilitic Antibodies—Donath-Landsteiner, Protective* The probable existence in syphilitic sera of antibodies to the spirochete, other than Wassermann antibody, has been discussed above in connection with spirochetal antigens There exists evidence of two additional types of syphilitic antibody —Donath-Landsteiner autohemolysins, and protective antibodies

The autohemolysins, which attach themselves to red cells on exposure to cold and subsequently cause hemolysis when warmed in the presence of complement, were discovered as a result of investigation of rare cases of paroxysmal hemoglobinuria Although the incidence of this complication of syphilis is extremely low, it is significant that Donath and Landsteiner (56) found the autohemolysin in the blood of 7 out of 93 paretics investigated, of whom only one had paroxysmal hemoglobinura, while Kumagai and Inoue (185) were able to demonstrate it in 7 out of 35 patients with late syphilis, none of whom had paroxysmal hemoglobinuria Since several investigators found that absorption of the hemolysin did not alter the response of the serum to the Wassermann test (reviewed in 204), it appears that the antibodies are distinct, the reverse experiment, with absorption by Wassermann antigen, would be desirable but has not been reported (204) This rather high incidence of low titer autohemolysins suggests that human erythrocytes contain an antigen other than the Wassermann antigen which might conceivably, after purification and concentration, prove useful as a serodiagnostic antigen for syphilis This possibility does not appear to have been investigated Nanba (228) has reported the production in rabbits of cold autohemolysins of Donath-Landsteiner type by the injection of suspensions of a variety of organs of various animals These experiments, which indicate a wide distribution for this antigen just as for Wassermann antigen, are reported in inadequate detail and need confirmation

The earlier literature on the immune protective mechanisms operative in syphilis, which has been reviewed by Chesney (41), did not establish the presence of circulating protective antibodies Recently Tani (281) has claimed the demonstration of these by a prolongation of the incubation period and reduction in the

size of the lesion in rabbits injected intracutaneously with mixtures of spirochetes (emulsion of rabbit syphiloma) and syphilitic serum, compared with control mixtures with normal serum injected simultaneously into the same rabbit. The irregularity of his data offer no justification for his conclusion, nor was Beck (11) able to demonstrate protective antibodies by the same technique Turner (289), however, by using a minimal dose of a standard frozen suspension of spirochetes, found that syphilitic serum prolonged the incubation period and decreased the size of primary skin lesions in rabbits Although the demonstration of protective antibodies might furnish an excellent verification test for syphilis, the delicate and laborious character of such procedures makes the development of useful applications of this technic appear unlikely. Early work on precipitins, opsonins, and skin reactive substances in the diagnosis of syphilis is reviewed by Eagle (71)

6. *Verification Tests*

(a) *Earlier Studies* There have been a number of attempts to eliminate incorrect diagnoses not only by improvements in the serodiagnostic antigens, but also by the development of verification tests based on differences between true and false positive sera Wassermann's (295) verification test, based on an alleged separation of antibody from antigen by filtration, is of historic interest only. Witebsky (307) obtained purified antibody from a malarial serum as well as from syphilitic sera by his method of heat dissociation, but since he failed to recover any from certain other false positive sera, it was concluded that his procedure might be used to distinguish those false positive reactions which were not caused by an antibody D'Alessandro and Sofia (48) also obtained purified antibody from certain false positive sera by a modification of this method, Bier and Trapp (20) from a leprous serum by a method involving dissociation by 15% salt, and the reviewer (50) from several false positive sera by the use of 15% salt plus ether Failure to recover antibody cannot be used as a criterion of a false positive serum unless the procedure used yields antibody regularly from even low titer syphilitic sera Since this was not shown for any of the above procedures, and since most false positive sera are of low titer, the failure to recover antibody from certain false positive sera was probably due to the low concentration of antibody in these sera rather than to the non-antibody character of the reacting substance—a concept for which there is little evidence

(b) *The Kahn Verification Tests* In 1940 Kahn (140, 141) introduced a verification test based upon the observation that the serum of syphilitic persons (148) or syphilitic rabbits (210) flocculated more strongly or in higher dilution with Kahn antigen at 37° C than at 0° C ("syphilitic" type of reaction), whereas the opposite ("general biologic" type of reaction) was true of the negative (150) or positive sera of non-syphilitic persons (149) or animals (147) Although the results obtained with this test were considered very encouraging, two years later (142) he offered another empirical test based on a difference in the degree of reaction in hypertonic and hypotonic saline (see also Green and Shaughnessy (98)) The latest verification procedure recommended by Kahn (144) involves several variations and permutations of these two tests

Chargin and Rein (40), employing the Kahn differential temperature verification test on 1,565 patients, found that in general syphilitic and non-syphilitic patients gave the syphilitic and general biologic types of reaction respectively However, 10 3% of treated syphilitics with weak standard Kahn tests gave the general biologic type of reaction It is apparent from these data, as well as from Kahn's papers noted above, that strongly positive sera quite regularly give the syphilitic type of reaction, but weakly positive sera, whether syphilitic or not, tend to give the other type of reaction De Groat (53) obtained the general biologic reaction in 6 malarial patients with transient positive standard Kahn tests In both the above studies the verification tests were performed in Kahn's laboratory No other laboratory has reported encouraging results Green and Forster (97) and Beveridge (19) concluded that the chief contribution of Kahn's verification test was the demonstration of increased sensitivity at higher temperatures The latter investigator obtained 28 general biologic reactions among 335 syphilitic and non-syphilitic sera, 14 of these were in proven cases of syphilis The occurrence of the syphilitic type of differential temperature Kahn verification test in a few false positive post-vaccinial sera has been reported by several investigators (201, 203, 284)

To the reviewer the evidence for the reliability of these Kahn verification tests is entirely inadequate That the tests are thoroughly empirical may be a reason for skepticism but not for repudiation, for the Wassermann test itself is irrational in that non-syphilitic tissue is the source of the antigen Kahn, however, seems to have presented these tests with excessive enthusiasm Thus, when he found that 10 low titer leprous sera gave the general biologic type of reaction, while 10 sera of higher titer gave the syphilitic type, it was concluded that the latter group might have syphilis (149), although the study was set up in order to test the procedure against these false positive sera rather than the reverse The several changes in procedure also lend no support to their reliability While it is conceivable that there may be some value in these tests, it is to be regretted that they have already been prematurely accepted by some as an established verification test (38), and have even been recommended for routine use in countries with a high incidence of endemic malaria (130)

This criticism of the Kahn verification procedures involves no reference to the Kahn Standard serodiagnostic test, which has long been one of the most respected flocculation tests

(c) *Other Empirical Differences* A difference in stability to heating, as was reported by Landsteiner (190) for natural and induced hemagglutinins, has been reported (184) for Wassermann and spirochetal antibodies, but this could not be confirmed (12, 73) No difference in thermal stability has been noted between the Wassermann antibody of syphilitic human and various normal animal sera (205, 269) Since thermal stability depends not only on the properties of the antibody but on the medium in which it is heated (8), and since the complement fixing and flocculating power of the same antibody may be differently affected (8, 260), it is not surprising that conflicting results have been reported Studies along these and other physico chemical lines are being carried out by Neurath and Beard (personal communication) It may be noted that Casals

and Palacios (39), performing complement fixation tests for rabies and encephalitis, were able to remove the interfering reactions of sera with normal brain antigen by means of moderate heating (60°–65°C.), which did not destroy the specific antibodies to the viruses

Cooper and Atlas are reported (31) to have found in the electrophoresis of 13 syphilitic sera in barbiturate buffer an absence of the "beta disturbance," which occurs in most normal sera, and it was suggested that "the electrophoretic pattern of a serum may be more specific for syphilis than either the Wassermann or the Kahn test." In view of the non-specificity of the changes in the electrophoretic patterns of serum which have been noted in a variety of diseases, it appears to the reviewer extremely unlikely that such a change will prove to be specfic for syphilis Another electrophoretic anomaly which has been observed is the formation of a fine precipitate in the region of isolated gamma globulin in the electrophoresis of a number of syphilitic and false positive sera (43, 50); its nature is unknown. Studies of the electrophoretic mobility and ultracentrifugal sedimentation of the antibody of a number of false positive sera (50) were unable to demonstrate any significant difference from syphilitic sera.

It has been noted (243) that syphilis, like a variety of infectious diseases, produces an increase in serum globulin. As was pointed out earlier in this review (II –4p), there is no clear evidence that hyperglobulinemia per se produces false positive reactions, it therefore does not appear reasonable to expect the albumin-globulin ratio to help to distinguish false positive reactions, except insofar as it may aid in the diagnosis of such diseases as lupus erythematosus

While it is not inconceivable that empirical differences of the above or other types may exist between syphilitic and false positive sera, it is to be emphasized that there is ample evidence that electrophoretic, ultracentrifugal, and immunochemical properties of antibodies to a given antigen in horses may vary among individual animals or even in the course of immunization of a given individual (reviewed in 136, p 536) Heidelberger and Kendall have shown that rabbit antibodies to such pure antigens as egg albumin (115) and pneumococcus Type III polysaccharide (114) are not homogeneous, different portions of the antibody (which vary in relative concentration during immunization) displaying different avidity for the antigen Antibody which formed particularly soluble complexes with antigen was subsequently termed "univalent" (117) In view of this heterogeneity of antibody, it is particularly important that any empirical procedure be tested on a large series of syphilitic sera, especially those of low titer, which might be expected to resemble most closely false positive sera Generalities which apply to a few dozen sera carefully studied in a scientific investigation may well find exceptions when applied to the thousands of sera encountered in routine testing

7 *Requirements of a Verification Test*

Although the evaluation of any new serodiagnostic procedure in this country has depended on its record in the Original Methods Evaluation Surveys, it would be well to point out that the requirements of a verification test are not identical

with those of a serodiagnostic test Since the causes of false positive reactions are multiple, there are probably a variety of substances causing false positive reactions in sera, and it would not be reasonable to expect any single verification test to distinguish all false positive sera It is also entirely possible that results obtained with malarial (or leprous) sera would furnish no indication of the value of a verification test in distinguishing the "normal" case with persistently positive reactions, which is the most perplexing diagnostic problem On the other hand, investigation of this latter group is clouded by the inevitable suspicion that syphilis may, after all, be present

To the reviewer it appears that the most important requirement of a verification test is that it should give no appreciable number of false *negative* reactions in cases of seropositive known syphilis—i e , that it should have a sensitivity in the Evaluation Surveys at least equal to that of the accepted serodiagnostic tests If it then gave a high proportion of negative reactions in an adequate series of "normal" or other types of false positive sera, the results would have some value This would be true regardless of the specificity shown by the test in the Evaluation Surveys, since a verification test, by definition, would not be used except on sera which were positive to the standard tests Encouragement in the hope that the non-specificity of the spirochetal antigen might extend to different sera from that of the Wassermann antigen is offered by the observations of Beck (12), who found that his spirochetal antigen was slightly less specific than his Wassermann antigen (1 6% and 1 2% false positive reactions, respectively), but *no sera were falsely positive to both tests* Considering the results of the 1941 Survey (240) from this point of view, it appears to the reviewer that the results obtained with Eagle's spirochetal antigen (75 9% sensitivity as opposed to 59 2 to 79 0% for 24 other complement fixation and flocculation procedures) are extremely encouraging in spite of 1 9% of positive reactions with normal sera

8 *Avenues of Future Approach*

The attempts to differentiate false positive from syphilitic sera may be grouped into empirical and immunological tests, none of which has yet offered a reliable method Empirical differences have been sought in stability to heat, solubility, and electrophoretic and ultracentrifugal characteristics of the reacting substances, as well as in the optimum temperature and salt concentration of the reactions To the reviewer the more promising and rational approach to detection of delicate differences between immunologically cross-reacting antibodies would involve immunological methods These include 1) purification of the antigen obtained from mammalian tissue (beef heart), 2) testing for entirely different antibodies produced in syphilis, such as (a) antibodies of the Donath-Landsteiner type, (b) protective antibodies, and (c) antibodies reacting with spirochetes immunologically as close as possible to the true virulent *Treponema pallidum,* and 3) dissociation of antibody from floccules, on the supposition that certain false positive sera react by virtue of physico-chemical abnormalities not involving dissociable antibodies

The Donath-Landsteiner and protective antibodies have not been studied

with reference to this problem, the dissociation of antibodies appears unpromising for reasons discussed above (Section III 6a) The most deserving of further work appear to be purification of Wassermann antigen and studies of spirochetes and their chemical fractions Spirochetal work will be greatly benefited if developments in the field of bacterial metabolism lead to the cultivation of true *Treponema pallidum* The encouragement by the reviewer of further work on spirochetes is based on no personal experience, but rather on the evidence that spirochetal antigens react with antibodies other than Wassermann antibody, and on the results reported on the reactions of these antigens with syphilitic sera. This enthusiasm may be tempered by the evidence that certain types of false positive sera (e g , malaria and possibly leprosy) cf Section III 4c) cannot be distinguished from syphilitic sera by antigens composed of unfractionated cultivated spirochetes.

A fourth immunological method, which has not been applied to this problem, is based on the fact that cross-reacting antibodies to a given antigen may be differentially absorbed by related antigens Thus Stuart (279) has shown that sheep cell agglutinins of different origin may be differentially absorbed by erythrocytes or other tissues of various species Encouragement in the applicability of this approach to the present problem is offered by the observation of Mackie and Anderson (205) that an acetone-soluble fraction of sheep heart (normally discarded in the preparation of the alcohol-soluble, acetone-insoluble diagnostic antigen) flocculated with non-syphilitic as well as syphilitic human sera Absorption of seropositive rabbit sera with this substance removed their capacity to react with further additions of the same antigen, but did not interfere with their reaction with Wassermann antigen. It is very likely that the various serodiagnostic antigens contain more or less of such substances It is possible that some false positive sera, especially those reacting to markedly different degree with various antigens, might contain large amounts of antibody to these contaminating antigens, which could be absorbed out

Since most false positive tests are weakly positive, a large proportion of them could be eliminated if the sensitivity of the serodiagnostic tests were set at a lower level This approach is impracticable since it would defeat the purpose of routine testing, which even now misses a certain number of cases of syphilis (80) The danger of false negative tests is illustrated by the occasional occurrence of congenital syphilis in children of seronegative mothers (297)

IV CLINICAL DIAGNOSIS OF FALSE POSITIVE CASES

1. Procedures Recommended in Suspected Cases

1) *Examination for syphilis.* The physician can begin to suspect a case of being false positive only after a meticulous and detailed history and physical examination have failed to elicit signs or symptoms of the disease, and then only if the patient appears to be honest and reliable With a history of possible exposure, it must be remembered that if biologic false positive reactions occur in virgins, they must also occur in that large body of adults who have had sexual exposures The suspicion of syphilis is necessarily greater in the latter group, but less so if the positive test developed without sexual exposure since a previous

negative test In taking the history, it is of the utmost importance to stress to the patient the danger to his future health if an omission from his history should lead to the withholding of treatment for syphilis An apparently false positive diagnosis may be based on a false negative history

2) *Search for basis on a false positive reaction* The physician must be alert to the various known causes of false positive reactions The only ones which are common in this country are malaria, infectious mononucleosis, certain types of respiratory infection, vaccination against small-pox, and possibly other inadequately investigated diseases such as measles, mumps, and infectious hepatitis Since the relation of false positive reactions to a number of common infectious diseases is not clear, any febrile disease occuring within three months preceding the test may be suspected as the cause of a false positive reaction, but is not essential to such a diagnosis

3) *Epidemiology* Serologic testing of the parents, siblings, and children of the patient is indicated, as well as investigation of the spouse and any other sexual contacts The occurrence of more than one seropositive person in a family is not proof positive of syphilis, for transiently positive tests have been recorded in several members of 2 families suffering from "bronchitis" (196, 312) On the other hand, in two studies (165, 182) of the incidence of syphilis in the spouses of known syphilitics, it was found that approximately half were free of the disease These series included all age groups, and so do not disprove the reasonable assumption that in young adults absence of the infection in the marital partner is strong evidence against the presence of syphilis

4) *Repeated tests* An initial positive serologic test for syphilis is always the indication for immediate repetition to eliminate the likelihood of technical error Unless the laboratory performing the test is known to be very reliable, it is desirable to have a positive or doubtful specimen checked in another laboratory As was noted earlier, the sensitivity of these tests in even the best laboratories varies so much from day to day (216, cf Evaluation Surveys 47, 240) that repeated tests fluctuating between positive, doubtful, and negative, are an indication only of a low titer serum, which may be syphilitic or not It is also desirable in a questionable case to have the serum tested by a variety of antigens, although discrepancies among such tests do not disprove the presence of syphilis Mahoney (207) has stated that discrepant serologic findings with a battery of tests are the rule rather than the exception in treated syphilis, but are not the expected finding in untreated syphilis of any appreciable duration and hence are not an adequate basis for the arbitrary diagnosis of syphilis

5) *Quantitative tests* Most false positive sera have weak reactions, in young adults, in whom acquired syphilis would exist in the early stages, such weak reactions are suggestive of a false positive test On the other hand, as with almost all the phenomena discussed in this review, the distribution curves of true and false positives may be expected to overlap, for as high as 3 8% of a series of 118 cases of secondary syphilis had a low titer (median 5 units Eagle complement fixation) (16) even though most secondary cases have the highest titers of all syphilitics, while over 10% of a series of cases of active late lues were seronegative (218) On the other hand, a high titer reaction, although stronger evidence of

syphilis than a weak reaction, is not adequate proof Suspected sera which are strong enough to be titered quantitatively should be followed with periodic quantitative tests in the same laboratory for weeks or months, since a false positive reaction may fall rapidly in titer, while untreated syphilis would not

6) *Period of probation* Since none of the available laboratory procedures can definitely distinguish false positive sera, and since occasional cases occur without obvious cause, the most important procedure in handling such cases is observation without treatment *A positive serologic test is not an emergency.* Although the results of treatment are best in early cases, delay of a few months in a case of latent syphilis is not likely to affect the outcome appreciably The one absolute contraindication to such delay is pregnancy, in which the risk to the fetus is not justified

Very few of the reported positive reactions following various infectious diseases persisted for more than three months, most of them having cleared within two weeks The Venereal Disease Control Branch of the U S Army has recently instituted the practice (290) of following serologically at 2–4 week intervals patients discovered to be seropositive following vaccination or an acute infection but having no conclusive history or clinical manifestations of syphilis, if the case remains positive at the end of 3 months, treatment is started This would seem to be a reasonable rule for the civilian practitioner Many of these cases will have lost their positive reactions within three months Whether to treat the persistently positive case as syphilitic will be further discussed below (Section IV 2)

7) *Cerebrospinal fluid* The testing of the spinal fluid in the absence of symptoms is, like the initiation of treatment, not an emergency, and should be deferred during the period of probation in which the patient's serology is being followed If the test becomes negative an unpleasant procedure will have been avoided If, however, the serology remains positive but it is decided to withhold treatment, a serologic test of the spinal fluid is indicated

8) *Supplementary tests* Most of the above procedures have been recommended by Moore and coworkers (217, 219) In addition they recommend a number of procedures which are desirable for the complete clinical study of these puzzling cases, but which cannot be expected to be of practical assistance except in very rare instances These include search for malarial parasites and for the characteristic leukocytes of infectious mononucleosis and determination of the heterophile antibody titer and sedimentation rate Other suggested procedures, such as the Kahn verification test and tests with spirochetal antigen and with such non-specific antigens as various bacteria, milk, and lecithin, may be worth incorporating into research projects in this field, but are not well enough established at present to be of value to the practicing physician

2 *The Persistently Positive Case*

Little help in diagnosis can be expected from the various laboratory procedures outlined immediately above The conclusion was reached that any seropositive patient without definite evidence of syphilis should ideally be followed for at

least three months without treatment, whether or not any known cause for a false positive reaction is present[7] Although a verification test would be desirable to eliminate the confusion, inconvenience, and psychic trauma of the probation period in the group of patients who become negative, they can easily be detected if the practitioner will cultivate a sufficiently high index of suspicion toward serologic tests, and will implement this with sufficient patience The persistently positive cases, however, will remain a difficult problem until a reliable verification test is available

Although such patients are undoubtedly being followed without treatment by a number of syphilologists, the only publication on an extensive series of this kind is from Moore's clinic (214) The justification for taking this responsibility appears to the reviewer to rest on several considerations 1) While accurate prognosis for untreated syphilis is impossible, it is estimated (221, 222) that approximately 1/3 will remain latent and 1/3 will undergo spontaneous clinical and serologic cure, with only 25% developing disabling or fatal disease This is borne out by the recent analysis of a series of autopsies on 380 patients diagnosed clinically or serologically as syphilitic (21, 256, 257), of these only 10% had demonstrable syphilitic lesions, and 20% fatal lesions Of the seropositive cases without clinical evidence of syphilis, only 20% had lesions (21) It is possible that many of these were false positive, but even if they are regarded as burned-out syphilis, the argument for withholding treatment remains equally applicable 2) It is known that present modes of treatment are considerably less successful in effecting cure of late than of early syphilis These asymptomatic questionable cases, if syphilitic, would have to be classified as either congenital or late latent, and hence fall into the relatively treatment-resistant group 3) Since syphilis in these stages is not contagious, there is no epidemiological indication for treatment (except in the case of pregnancy) 4) Finally, antisyphilitic treatment is dangerous and should not be given unless the risk is justified by the actual existence of syphilis (219) This consideration may be largely eliminated if the recently discovered value in the treatment of early syphilis (208) of the less toxic drug, penicillin, proves applicable to the latent stages of the disease This would not, however, eliminate the important social, psychological, and economic reasons for avoiding a false diagnosis of syphilis

In spite of these considerations, it is necessary to note the statement that "Of patients with proved syphilis of various types, at least one-third of the men and one half of the women can give no story of early symptoms" (219), although statistics in support of this are difficult to obtain The responsibility for withholding treatment of a case with a persistently positive serologic test should therefore be taken only by a syphilologist of experience The hazard of this responsibility will be clarified by the future course of such cases which are now being followed

[7] This recommendation must be modified by other considerations, such as the syphilophobia of some patients which would lead them to grasp too tenaciously at the hope of a false positive reaction

V. SUMMARY

The serologic tests for syphilis are subject to marked variations in sensitivity, these largely account for the discrepancies in published reports on the incidence of biologic false positive tests in various diseases Many of the cases reported have undoubtedly been technical false positives based on unreliable earlier Wassermann tests Standards of performance of Wassermann (complement fixation) and flocculation tests have been elevated by international and United States Serologic Evaluation Surveys, but fluctuation in day to day results on weakly positive sera is still inevitable In order to avoid technical false positive reactions, it is desirable to obtain more than one positive test before considering a case biologic false positive.

The incidence of transient positive tests following acute infections depends largely on the frequency of testing during the acute and convalescent stages. Although post-infectious or post-vaccinial positive reactions occasionally last as long as 3 months, most become negative within a few days or weeks Since it is customary to perform serologic tests on hospital patients only on admission, at which time acute infections have not fully developed their antibodies, it is likely that the ability of many common infections to lead to false positive serologic tests is grossly underestimated Those causes of transient positive reactions (malaria and vaccination) which have been tested at short intervals have shown some degree of reaction in nearly 100% of the cases, but the majority of these were only 1 or 2 plus reactions, and would ordinarily be reported as negative or doubtful Similar studies would be desirable in a variety of common infectious diseases.

False positive serologic tests are common (more than 10% of cases) in leprosy, malaria in the acute stages, infectious mononucleosis, vaccination against smallpox, rat-bite fever due to Spirillum minus, relapsing fever, lupus erythematosus, and possibly certain types of atypical pneumonia There is no reliable evidence that the serologic tests are significantly affected by pregnancy, menstruation, scarlet fever, jaundice (other than infectious), subacute bacterial endocarditis, tuberculosis, or hyperproteinemia, in spite of earlier reports Inadequate data are available on measles, mumps, infectious hepatitis, lymphopathia venereum, chancroid, and many other diseases

Transient false positive reactions may occur in apparently normal individuals without recent illness, and in cases of some diseases in which the incidence is so low as to suggest that the relationship may be coincidental It has recently been suggested that even persistently positive reactions may occur in non-syphilitic patients Since a large proportion of seropositive patients have no syphilitic lesions at autopsy, it is entirely possible that many seropositive persons without a history or signs of the disease have been mistakenly diagnosed and treated for latent syphilis Surveys of normal populations have shown that the incidence of false positive reactions is only a small fraction of 1%, but in large serologic dragnets the number of innocent victims may be large, and the psychological, social, and legal consequences to the individual may be serious

Since low titer syphilitic sera may show discrepancies between the results ob-

tained with various test antigens, and fluctuation in apparent reactivity of successive sera, these are not adequate criteria for considering a positive serum false

The various complement fixation and flocculation tests for syphilis are antigen-antibody reactions The lipid antigen is widely distributed in human and other mammalian tissues, and is an effective antigen for forming antibodies if mixed with a foreign protein before inoculation (hapten phenomenon) It is not clear whether the Wassermann antibody is formed in response to Wassermann antigen from the organisms or to tissue antigen rendered active by the spirochete If the latter hypothesis is correct, no difference would be expected to exist between the Wassermann antibodies in syphilis and in other diseases

Some of the false positive reactions may be eliminated in the future by purification and improvement in specificity of lipid antigens of the Wassermann group, but there is no reason to expect all false Wassermann antibodies to differ in any given respect from the true antibody Attempts to find consistent empirical physico chemical differences between syphilitic and false positive sera have thus far failed To the reviewer the most promising approach to the problem is the detection of antibodies to antigens of the spirochete other than Wassermann antigen Although virulent Treponema pallidum has not yet been cultivated, certain strains of cultured spirochetes have been found to be antigenically distinct from Wassermann antigen in the complement fixation test, and to detect syphilitic sera with encouraging regularity The specificity of such a spirochetal antigen was found in the 1941 U S Serologic Evaluation Survey to be too low to permit its use as a serodiagnostic procedure, but this does not eliminate its potential value as a verification test Further work is indicated

Measures are recommended for the handling of seropositive cases which have no clinical basis for diagnosing syphilis A positive serologic test is not an emergency The most important procedure, in the absence of pregnancy, is a probationary period of at least 3 months before starting treatment While many false positive tests will be revealed as transient during this period, there is no verification test available today to help in the diagnosis of those which remain positive

The author gratefully acknowledges the valuable suggestions of Dr E A Kabat, Mr A Harris, and Dr H Eagle

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OLD, INTERMEDIATE, AND CONTEMPORARY CONTRIBUTIONS TO OUR KNOWLEDGE OF PANDEMIC INFLUENZA[1] [2]

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The title for these lectures was submitted about two months ago before I had a very clear idea of how my subject matter was going to develop As it has turned out it is quite a bit too broad and collective in its scope and implies a general acceptance of some of the things that I am going to present For this reason, before starting it might be well for you to make a mental note as follows "The general group of investigators of and philosophyzers on the subject of influenza do not necessarily endorse or agree with any or all of the views expressed herein " The facts that I shall present, however, I believe are largely established and agreed upon

"Pandemic," according to Stedman's Medical Dictionary, is applied in noting a disease affecting or attacking all or a large portion of the population of a region, a disease extensively epidemic Nothing in the definition implies degree of severity However, in these lectures I intend using the term as it is most widely applied in current influenza parlance to indicate severity as well as extent of distribution By "pandemic influenza" is meant a severe disease of the type that occurred during 1889–90 and during the autumn of 1918 By "interpandemic influenza" is meant the milder type of influenza occurring between the pandemics at roughly two year intervals or oftener

Since influenza is an old disease it would be unrealistic to assume that all knowledge concerning it has been derived in modern times Some of the older observations have their applications and usefulness even today, especially as they concern the epidemiology of the disease

EARLY CONCEPTIONS OF THE EPIDEMIOLOGY OF INFLUENZA

We are prone to consider the speed of spread of influenza as a modern attribute and to explain it on the basis of modern rapid means of transportation such as railroad trains, airplanes, etc Strangely enough, though, the disease had a reputation for rapid and widespread diffusibility even several centuries ago before any of the modern means of conveyance were in use. A paper which dealt extensively with the epidemiologic views of the times and which antedated any of the modern means of transportation was one by Robert Jackson (1)

[1] Thayer Lectures presented at The Johns Hopkins Medical School March 16 and 17, 1944

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dealing specifically with the pandemic of 1789 Even in those ancient times, according to Johnson's account, influenza seems to have spread like wildfire

Now Johnson in his definition of influenza characterized it among other things as "a disease capable of being propagated by contagion" In spite of this conception he could not completely rationalize the speed of its dissemination on the basis of transmission by contact alone On this point he wrote as follows "The present received opinion is that this species of Catarrh (Influenza) arises from contagion, which possibly may be true yet to my mind it appears no easy matter to conceive how the disease can spread so far and wide in so short a space of time as we perceive it does, or how it can affect persons many miles apart, at the same time, where there had been no previous direct or indirect intercourse—if propagated only by a matter arising from the body of a man labouring under it"

Johnson disagreed violently with earlier writings, which he attributed to Cullen, in which appeared the statement that influenza "has seldom appeared in one country of Europe without appearing *successively* in every other part of it, and, in some instances has been even *transferred* to America, and has been spread over that continent as far as we have had opportunities of being informed" He objected particularly strenuously to Cullen's use of the words "successively" and "transferred," maintaining that the evidence indicated only that influenza appeared later in some parts of Europe and in America than it had in other parts of Europe The speed of its spread nullified any implication that it had been "transferred" He contended that the fact that the disease was known to have been appearing simultaneously in Europe, Africa, the Isle of Bourbon and in ships at sea was sufficient evidence that its successive appearance in various other places did not have to be explained necessarily on the basis of contagion.

Johnson rationalized his views concerning the multiplicity of foci of origin of influenza during a pandemic by contending that, "The morbific matter exciting the disease must have originated at some time, and somewhere, and a cause like to that which gave rise to it in any one country, at any one point of time, might produce it in another country at the same time, under similar circumstances"

He summarized his conception of the epidemiology of influenza in the following statement "Did the Influenza depend upon a specific contagion it must always exist, or we cannot possibly ascribe it to such a cause The small pox, the venereal disease, etc , never intermit but the Influenza has become extinct, and again broke forth upon the world after a period of more than 4 score years" (1591–1675)

He continued "I do not assert, nor do I wish to be understood to mean, that the Influenza is not at all contagious on the contrary I am possessed of facts which prove in the most incontestable manner, that it may be, and often is propagated from one person to another by means of contagion But I mean, and the arguments which I have adduced, I trust, will warrant the conclusion, that the disease often does arise from some viscious quality of the air, or exhalation in it, as well as from a matter arising from the body of a man labouring under disease."

It is apparent from these statements that Johnson conceived influenza to be a disease that was initiated by meteorological or atmospheric influences but that, once started, was capable of propagation from sick to well by contact He had the same difficulties, however, as our present-day epidemiologists in explaining the origin of his first cases, though he was not, as we are, handicapped by having to make his views fit the knowledge that the disease has a specific microbial cause

Johnson was still thinking very much in the terms of Hippocrates, Boerhaave, and Sydenham, and drew heavily upon their older views in formulating his concept of the epidemiology of influenza He recognized four causes as contributing to the disease and at least three of these had to be operative at the inception of an epidemic He referred to these four causes in the nomenclature of the times as the remote, the predisposing, the exciting, and the proximate The remote cause was thought to be "some viscious quality of the air" and bore a relationship to the seasons and meteorological conditions The predisposing cause was defined as "that which renders the body liable or capable of being affected by disease when the exciting cause is applied " The exciting cause was considered to be "that external circumstance which kindles the fever, to wit, the morbid miasma, or contagion " The proximate cause, in reality probably an effect, was the inflammatory reaction in the respiratory tract responsible for the signs and symptoms of illness exhibited by the sick individual The coincidental inter-relationship of these various causes was held accountable for the initiation of an influenza outbreak According to Johnson's conception of the epidemiology of the disease, when they were operative at one geographical location on the earth they were likely to be operative simultaneously, or almost simultaneously, at many other locations

Watson (2), writing concerning the 1847 pandemic which was also pre-modern, said "What I wish to point out now is the fact that the Influenza pervades large tracts of country in a manner much too sudden and simultaneous to be consistent with the notion that its prevalence depends exclusively upon any contagious properties that it may possess "

I have gone into some detail in outlining the views, opinions, and observations written concerning a pre modern pandemic of influenza for two reasons In the first place I wanted to point out that influenza spread with unbelievable rapidity even before we had modern means of rapid transportation to blame for its speedy and widespread diffusion Secondly I wanted to indicate the rather ingenious devices by which this unbelievably rapid dissemination of a disease was rationalized by thoughtful medical people in those olden times To me it seems that we may be missing something of significance in the epidemiology of influenza by placing our entire confidence in the conception that every case of influenza, especially at the outset of a pandemic, must of necessity spring from some preceding case of the disease I shall have more to say of this later

THE INFLUENZA PANDEMIC OF 1889–90

The first pandemic of influenza in the bacteriological and statistical era was that of 1889–90 There seems to be general agreement that this pandemic bore

most of the earmarks of the greater one that followed it in 1918 except for its lower fatality Vaughn (3) who studied the 1918 pandemic and thoroughly reviewed the literature dealing with that of 1889 wrote in his monograph on influenza that, "The longer one studies the observations made in 1889–93 the more firmly convinced one becomes that the recent pandemic (1918) was identical with the former in practically all of its manifestations"

The main finding of value derived from studies of the influenza pandemic of 1889–90 was the discovery of the so-called influenza bacillus by Pfeiffer Pfeiffer had seen the bacilli in the sputum during the spring of 1890 but his actual work on influenza did not begin until November 1891 In the beginning Pfeiffer was unable to subculture the bacilli though they produced an abundance of small colonies on agar plates directly smeared with sputum Later he announced that he had overcome the difficulty of subculture by adding blood to his culture medium (4) In 1893 he published a full account of his work on influenza giving complete details of methods for isolating and maintaining the bacillus in pure culture (5) With the publication of Pfeiffer's work his findings received widespread confirmation during the short remaining period that influenza was widely prevalent

Pfeiffer believed that the bacillus he had discovered was the cause of influenza because, according to his observations, it was present in all cases of the disease studied, it was not present in normal individuals unless they had recently recovered from influenza, and it was in intimate association with the lesions of the disease Pfeiffer's views were widely accepted and it is safe to say that a majority of the students of influenza at the time believed the cause of influenza had been discovered

With more thorough studies of the incidence of Pfeiffer's bacillus after the pandemic had passed, however, doubts arose in the minds of some investigators as to the true relationship of the organism to influenza It was found, for instance, to be present in the respiratory tracts of certain apparently normal individuals and it was also encountered not infrequently in other infectious diseases, especially whooping cough, measles, and tuberculosis Furthermore the bacterium was sometimes not present in cases that looked clinically like influenza Findings such as these, though they tended to weaken the case for Pfeiffer's bacillus, did not constitute insurmountable objections because healthy carriers were not unknown in other diseases and there was no certainty that what appeared clinically to be influenza between pandemics was actually the same disease that Pfeiffer had studied Despite the doubts that were raised, in the years following Pfeiffer's work, the bacillus he had discovered was quite generally regarded as the probable cause of influenza.

THE INFLUENZA PANDEMIC OF 1918

The 1918 pandemic of influenza was without doubt the most catastrophic outbreak of infectious disease of modern times. It killed about 21,000,000 people and probably 25 times that many sickened of it The exact date and site of its onset are subjects about which there seems to be no conclusive information

Prior to 1918 there had been small outbreaks of what appeared clinically to be influenza with epidemic tendencies in various parts of the world In all of these the question is open as to whether they were in fact influenza So far as can be told from the literature, there was no one point in the years immediately preceding 1918 where it might be said that influenza, which had previously been nonexistent, started at a focus and spread throughout the world (3)

A mild outbreak in the spring of 1918, which has become generally known as the first wave, is believed by most epidemiologists to have been the immediate forerunner of the great autumnal outbreak which swept over the entire world with such deadly effect The first wave received especial prominence in Spain where it was said to have been sudden in its appearance, brief in its course, and to have subsided without leaving a trace In April, at about the same time that the Spanish epidemic was occurring, American, British, and French troops in France as well as the civilian population were suffering from extensive outbreaks of the same disease The disease is stated to have spread rapidly into Germany and the rest of Europe It is not known whether the first wave of European influenza was autochthonous or, if not, from where it was introduced In England, the first wave appeared in June and was composed for the most part of mild cases (6) In the United States, sporadic outbreaks of what clinically appeared to be influenza had been occurring in various army camps during the winter of 1917–18 However, in March of 1918 the disease is stated to have passed from the sporadic to the epidemic stage and many of the camps reported increases at this time (7) The disease was of course prevalent among the civilian population during the spring of 1918 but the incidence was lower In Japan and China also a mild influenza epidemic prevailed in the spring of 1918 (8) The first wave thus seems to have started simultaneously, or almost so, in three widely separated regions of the earth, namely, Europe, the United States, and the Orient No one has been very successful in tracing it from one area to the other and the best thought seems to be that at least three separate foci of origin were involved

The spring wave of influenza does not seem to have been highly diffusible because it reached only limited regions of Africa and supposedly largely missed South America Even Canada was but slightly affected It was almost everywhere very mild and although the morbidity was often high, sometimes amounting to 50 per cent or more of the invaded population, the case fatality was exceedingly low (6)

The second wave, which proved to be extremely lethal, struck simultaneously in many parts of the world It is generally stated to have appeared in Europe during the last week in August and in the United States at about the same time Between the first and middle of September scores and hundreds of foci appeared in various army camps, naval stations, and civilian communities in this country By the first week in October the pandemic was full blown throughout the entire world with the exception of a few islands and Australia The height of the pandemic so far as this country is concerned was the fortnight between October 12th and 25th

In the second wave, though there were many instances of the same mild type as in the first, a different manifestation of disease became prominent This took two forms a) cases which started immediately with an acute pulmonary inflammation resulting in lung edema, violet cyanosis and death within a few days, and b) cases which developed on the 4th or 5th day of an ordinary influenza a definite bronchopneumonia, running the usual course of the primary bronchopneumonia of pre-pandemic times and being followed accordingly, either by death or by a long convalescence (9)

Most epidemiologists are of the opinion that the 1918 autumn pandemic arose at one or two sites and from these spread throughout the world in a little over a month's time It is quite commonly accepted, and there is evidence to support the opinion, that the pandemic so far as this country is concerned started in or near Boston (3, 6) The cases responsible for the Boston infection supposedly came from Europe where the pandemic got under way very little if any earlier than it did in the Boston area The spread from Boston to other parts of the United States is explained as resulting from transfer of the infection by cases moving about among the civilian population or by cases among military personnel being transferred from one camp to another The speed of spread is explained on the basis of the speed of available transportation for these infected cases

While, if one chose to believe that influenza spread from sick to well at the very first available opportunity, it was possible to visualize the pandemic progressing as rapidly over the country as it apparently did, the speed with which it was disseminated actually seemed almost too rapid to be true For instance, among the army camps the disease became well established in 9 during the very first week of the pandemic These camps were in states as variously located geographically as Massachusetts, New York, Virginia, South Carolina, and Georgia The second week of the pandemic saw 13 more camps involved in states geographically as widely separated as Texas, Kansas, Louisiana, Illinois, Maryland, and Washington (6) It is quite true, of course, that so far as speed of transportation is concerned it is perfectly possible that any of these localities could have been visited several times by individuals from infected regions during even the first few days of the pandemic On the grounds of opportunity for transmission by contact therefore the possibility cannot be denied that the spread of the disease, rapid though it was, is entirely explainable on the basis of case to case transfer However, if one chooses to accept this explanation certain discrepancies enter to spoil the perfection of the explanation These have to do largely with certain flukes in distribution, certain skips of large bodies of population, etc I shall mention only a few of these to indicate to you what I mean

Taking the week of highest mortality as a criterion of the time of occurrence of true pandemic influenza in a community we find places as widely separated as Boston and Bombay having their peaks in the same week while New York only a few hours by train from Boston did not have its epidemic peak until 3 weeks later (6) It can hardly be reasoned that no one traveled from Boston

to New York for 3 weeks during September of 1918 Omaha, Memphis, Baltimore, Montreal, and many other places less rapidly accessible to Boston than New York had epidemic peaks a week or more earlier than New York In like manner, Seattle, Los Angeles, and San Francisco had their epidemic peaks a week or two earlier than Pittsburgh which is just an overnight run from the infected eastern seaboard cities

Another of the observed features of the autumn wave that is not easy to rationalize on the basis entirely of contact infection is the difficulty of explaining its relatively slow diffusion over comparatively short distances as compared with its unbelievably rapid spread over geographically wider areas In many respects the epidemiologist had an easier time getting the pandemic disease transferred from Boston to Chicago, for instance, than he did getting it the remaining 38 miles from Chicago to Joliet If pandemic influenza spreads from sick to well by contact at the first opportunity as it is assumed to do in explaining the rapidity of its spread over long distances, then it should diffuse with reasonable rapidity over shorter distances Yet it does not apparently do this In Connecticut, for instance, the disease took 3 weeks in getting from New London County in the southeast corner of the state to Fairfield County less than 100 miles away in the southwest corner (6) Then again, in the vicinity of Chicago the northern suburbs of the city were attacked almost a month earlier than the communities of Harvey just 20 miles south and Joliet 38 miles southwest of the city (6) When one considers the large amount of daily travel into and out of Chicago from these neighboring towns it is quite obvious that the mere opportunity for infection by means of cases carried on available transportation facilities furnishes an inadequate explanation for the rapidity of spread of influenza

In spite of apparent discrepancies of the type just called attention to, the opinion that direct and indirect transmission from man to man can account for the observed epidemiological picture of pandemic influenza is generally accepted Periodically, careful observers have doubted the correctness of this hypothesis but have never been able to demonstrate clearly another to take its place W T Vaughn (3) in his monograph on influenza rather well summarized present-day views concerning the spread of pandemic influenza by man to man contact when he wrote, "Today we assume the correctness of the hypothesis, and pass on to consideration of other subjects of more recent development"

At any rate, no matter what the correct explanation for the wide dissemination of the 1918 autumn pandemic of influenza was, there is no doubt that the disease became very extensively distributed in short order This second wave differed from the first in certain epidemiological features in that it was more severe, more widespread, of greater dispersive power, and in some places at least of a different age incidence

There seems to have been the greatest reluctance in designating the second wave, in the beginning, as influenza and various circumlocutions were resorted to It was referred to variously as epidemic bronchopneumonia, epidemic respiratory infection, unidentified pandemic disease, and a number of writers expressed their sense of difference by placing the name influenza in quotation

marks (6) Many clinical observers frankly declared that the autumn 1918 disease was new to them These statements were the more impressive because they were made less than 3 years after the occurrence in 1915–16 of what at the time had been designated as an "extensive outbreak" of "influenza" They serve to emphasize the differences, both clinical and pathological, existing between pandemic and interpandemic influenza

Thanks largely to the careful house to house surveys conducted by Frost (10), Frost and Sydenstricker (11), Vaughn (3), Winslow and Rogers (12), and others, the data accumulated by the Army and Navy, and the accurate statistical treatment of the material, we have a very clear and probably true picture regarding the morbidity and mortality of the autumn pandemic as it occurred in this country According to the various surveys, the attack rate averaged between 20 and 30 per cent though there was considerable variation For instance, Frost's figures show a variable incidence ranging from 15 per cent for Louisville, Kentucky, to 53 per cent for San Antonio, Texas The mortality rates for different communities were also quite variable Thus Frost's data on case fatalities ranged from 3 1 per cent for New London to 0 8 per cent for San Antonio Vaughn's survey in Boston gave a case fatality of 2 47 per cent In some of the large army camps the case fatalities were very high (over 7 per cent for Camps Sherman and Cody) The average case fatality for the country as a whole probably approached 2 per cent

The highest attack rates occurred in the ages below 15 years and thereafter a decline in incidence took place The case fatality was high in infants, low in children, and rose again in young adults In the aged it was high The extremely high rate in the age group 20–40 resulted in a mortality curve for the autumn pandemic that was strikingly different from similar curves for interpandemic outbreaks of influenza

With all of the observed clinical and epidemiological evidence pointing to the likelihood that the 1918 pandemic influenza was highly contagious and spread from sick to well easily and apparently at the very first available opportunity one would anticipate that proof of its contagiousness by transmission tests in human volunteers would be extremely easy However, such did not prove to be the case and in not a single controlled experiment was it possible to demonstrate the transmissibility of the disease The most carefully planned and conducted experiments were those carried out by the U S Navy and the U S Public Health Service In the series of experiments conducted in Boston (13) during November and December of 1918, 62 volunteers between 15 and 34 years of age were used, 39 of these had no history of having had influenza at any time although apparently some degree of exposure had occurred Filtered and unfiltered secretions from the upper respiratory tracts of patients with typical influenza were sprayed into the noses and throats and instilled into the eyes of some of the volunteers, direct swabbing from nasopharynx to nasopharynx was resorted to in the cases of others, and in one experiment freshly drawn citrated blood was injected subcutaneously The results were summarized as follows. "In only one instance was any reaction observed in which a diagnosis of influenza

could not be excluded, and here a mildly inflamed throat seemed the more probable cause of the fever and other symptoms Nothing like influenza developed in the other volunteers " In an attempt to imitate nature more closely, 10 volunteers were exposed to cases of acute influenza in hospital wards Each volunteer was placed very near the patient, shook hands with him, chatted with him for 5 minutes, after which he received the patient's breath full in his face 5 times while he inhaled, and finally the patient coughed 5 times directly into the subject's face Each volunteer did this with each of 10 different patients, all of them acutely ill for not more than 3 days All cases of influenza used were typically ill acute cases selected from a distinct focus or outbreak of disease None of the volunteers developed the disease

A second series of human experiments was carried out in San Francisco (14) with 50 volunteers during the same period, and similar negative results were obtained

These two groups of experiments were considered to show that the requirements for the transmission of influenza from man to man, such as apparently exist commonly under natural conditions, are not readily imitated experimentally The failures were thought to be due either to the choice of immune volunteers, the choice of the wrong period for transmission, the choice of the wrong chief seat of the causative agent, or the choice of the wrong avenue of entrance to the body of the victim The experiments have done little or nothing to alter the view that the 1918 pandemic influenza was a highly contagious entity and was probably in the vast majority of cases transmitted directly from case to case—no other opinion explained the observed features of influenza epidemiology as well

IMMUNITY DURING THE 1918 PANDEMIC

The problem of immunity in influenza received a great deal of consideration during the 1918 pandemic and a number of clinical observations on the subject were made The succeeding waves that followed one another between the springs of 1918 and 1920 furnished admirable opportunities for studying the problem under natural conditions too, providing of course that each wave had a similar basic etiology

Because the presence or absence of an immunological relationship between the first and second waves of the 1918 influenza has an important bearing upon a phase of the subject that I want to discuss later on I should like to cite several examples dealing with this point

The Annual Report of the Surgeon General of the Navy for the year 1919 says in part that, " many men of the Navy who had influenza in the spring or summer of 1918, while in European waters, escaped during the later epidemics (winter 1918–19) both in Europe and the United States The British Grand Fleet experienced the same thing with few exceptions those men who contracted influenza in May and June were not attacked during the more fatal epidemics in October, November, and December The conclusion is that mild attacks earlier in the year, as a rule, conferred immunity against the more fatal type of

the disease which prevailed subsequently" With regard to the experience in the British Navy, Dudley (15) has pointed out that the crews of only certain ships were affected by the first wave, the crews of others escaping the infection During the second wave the attack rate on the ships that had had the earlier infection was about 25 per cent while on those ships that escaped the first wave the attack rate was about 50 per cent

In most army groups the outfits were moved about too much and transferred too frequently to furnish reliable records as to an immunological relationship between the two influenza waves in 1918 There are, however, large numbers of isolated records involving relatively small numbers of individuals For instance, Gibbon (16) writes that of 400 cases of influenza hospitalized from among the 2000 troops under his care no cases admitted in June, July, or August were readmitted in October, November, or December, and no cases admitted in either of those periods were readmitted in February of 1919 Dopter (17) reports recurrent epidemics in a French army division of which he was surgeon in 1918 During the spring wave towards the end of April only the infantry regiment of the division was attacked, the artillery regiment escaping infection In the fall a group of heavy artillery was attached to the division bringing influenza with it The disease spread but only those who had come through the first wave unattacked were very seriously ill in the second V C Vaughn (7) cites the experiences of the 2nd Infantry Regiment, U S Army, which underwent influenza in June of 1918 in Hawaii before being transferred to Camp Dodge about August 1st When the severe second wave hit Camp Dodge in September–October the 2nd Regiment was only slightly affected though the attack rate for the camp as a whole was about 33 per cent and the case fatality 6 8 per cent Probably the most impressive example of immunity among troops is that related by Vaughn (18) for a division stationed at Camp Shelby The division numbered about 26,000 and in April 1918 underwent a mild influenza causing about 2,000 cases Vaughn comments as follows on the subsequent history of the division "This was the only division that remained in this country without change of station from April until the fall of 1918 During the summer this camp received 20,000 recruits In October, 1918, the virulent form of influenza struck this camp It confined itself almost exclusively to the recruits of the summer and scarcely touched the men who had lived through the epidemic of April Not only the 2,000 who had had the disease in April, but the 24,000 who apparently were not affected escaped the fall epidemic It appears from this that the mild influenza of April gave a marked degree of immunity against the virulent form in October"

Certain information deriving from civilian populations also indicates an immunological relationship between the first and second waves of influenza Thus Malone and McKendrick (19) observed in Calcutta that three institution populations who underwent infection during the July wave passed through two later waves in December 1918 and February 1919 without contracting the disease a second time They believed that their evidence indicated an immunity lasting for at least 9 months The Inspector General of Health in Spain (2) reported that

those cities which had the disease in May 1918 suffered lightly in the autumn of that year, while others of the large cities which had been spared in the first invasion suffered most in the second V C Vaughn (18) has pointed out that among the large cities in the United States having a low death rate during the autumn wave of influenza were a number that had reported an unusually high incidence of influenza and pneumonia in the spring Jordan (6) has called attention to the fact that the attack rates in English towns during the autumn wave were only about half those prevailing in towns in the United States and comments on the temptation to account for the differences on the basis of the more sharply defined and extensive first wave which prevailed in England having conferred a more extensive immunity W T Vaughn (3) in studies deriving from his house to house canvasses in Boston found only 4 instances of more than one attack of influenza among 1,971 cases occurring in his series between March of 1918 and August of 1919

It is quite apparent, I believe, from the examples I have cited that the mild first wave of the 1918 influenza conferred considerable and definite protection against the severe second wave There are some examples that might be derived from the literature which fail to show a clear-cut immunological relationship between the two waves My reason for calling detailed attention to the examples indicating a relationship and neglecting those that do not is that, in a case where one is seeking to show a positive relationship between two conditions of unknown etiology, a positive correlation is, because of diagnostic uncertainties, of much more value in indicating the true relationship than is a negative one

The question of whether either the first or the second wave of 1918 influenza conferred any lasting immunity against that which recurred in 1920 can be answered quite confidently in the negative The figures derived from personal canvasses made by Frost (20), Vaughn (3), and Jordan and Sharp (21) agree in showing that the attack rates during the 1920 outbreak were not significantly different among those with a history of influenza in 1918 than they were among those giving no history of influenza in 1918

It may be said in summary then that evidence from the 1918 pandemic indicates that an attack of influenza probably imparts some measure of protection over a period of a few months but that, assuming the 1920 outbreak to have been etiologically similar to the 1918 influenza, after a year or more the presence of immunity in a sizable, previously affected population is difficult or impossible to demonstrate

STUDIES OF THE ETIOLOGY OF THE 1918 PANDEMIC

From the time of Pfeiffer's announcement of its discovery in 1892 to 1918 *Hemophilus influenzae* was quite generally regarded as the agent responsible for epidemic influenza Because of this general belief, much of the huge volume of work done during the 1918 pandemic was concerned with a further study of the relationship of this bacterium to the disease The results obtained were frequently confusing and contradictory, which is not surprising when one con-

siders the fastidious character of the organism and the technical difficulties associated with its isolation from the respiratory tract The bewildering variety of bacteria always present on the mucous surfaces and in the tissues of influenza patients constituted a serious difficulty to the isolation of the none-too-robust Pfeiffer bacillus if it did not happen to be one of the predominant forms present. As a number of investigators pointed out too, the Pfeiffer bacillus was sometimes present in one portion of the respiratory tract but absent in others Jordan (6) called attention to the fact that the organism might be rare or absent at one stage of the illness and very common at another The methods used, the frequency and intensiveness with which observations were carried out, and the bacteriological experience and skill of the investigator were often determining factors in deciding the percentage of positive demonstrations of the bacterium in any given outbreak under study

To me, one of the most suggestive and interesting observations deriving from the bacteriological studies of the 1918 influenza was the marked difference between the incidence of Pfeiffer's bacillus found in the first and second waves by individual investigators where the matter was studied The findings of almost all were in agreement that the Pfeiffer bacillus was either absent or of low incidence in cases of the first wave and abundantly present in cases during the second wave Thus Sobernheim and Novakovic (22) found Pfeiffer's bacillus to be practically absent from the early cases whereas in the second wave it was found in pure culture in a large majority of the cases investigated (18 out of 23) Fildes, Baker, and Thompson (23) who failed to find influenza bacilli in cases during July and August found them during the autumn wave in the sputum of 12 of 15 uncomplicated cases and in practically all their post-mortem material McIntosh (24) who failed similarly in the summer found Pfeiffer's bacillus in the autumn in 8 of 12 examinations of the nasopharynx in uncomplicated cases, and in the sputum of 21 of 25 cases with bronchopneumonia Michaelis (25) who failed to find *H influenzae* in the first week of the summer wave found it with increasing frequency later Fraenkel (26) failed to find the influenza bacillus in the summer epidemic but in the autumn found it in 8 of 11 autopsies Hicks and Gray (27) did not find the organism in the summer epidemic although in the autumn wave, using exactly the same methods, they found it readily and frequently McMeekin (28), in Australia, found the Pfeiffer bacillus entirely absent in the first wave there but abundantly present in the second

The experience of Opie, Blake, Small, and Rivers (29) in this country was similar, in a way, to the instances just cited They found that the incidence of Pfeiffer's bacillus in normal individuals from isolated communities, or in groups free from respiratory disease prior to the occurrence of the 1918 autumnal epidemic, was relatively low (10–20%) but that before the fall epidemic, in groups in which bronchitis and pneumonia were fairly prevalent, the incidence was higher (25–50%) During the epidemic the incidence rose to 95 per cent

I believe it can be safely said that, so far as the bacteriology of the first wave of the 1918 influenza epidemic can be used as a criterion, Pfeiffer's bacillus was not demonstrated with enough frequency to support its claim as the causative

agent Its presence probably about coincided with its distribution in healthy persons at the time that the first wave appeared Its incidence during the severe second wave, however, seems to have been quite another story In addition to the observations I have just cited indicating the widespread presence of *H influenzae* in the autumn wave, might be mentioned the work of dozens of other investigators who also found the organism in all, or almost all, of the cases of the second wave that they studied Reports by well-known bacteriologists of the isolation of the influenza bacillus from 70 to 90 per cent of the sputa they examined or from 90 to 100 per cent of their post-mortem material were extremely common This was especially true during the early part of the autumn wave Later on, and particularly in certain sections of this country, the incidence of Pfeiffer's bacillus found in undoubted cases of pandemic influenza was lower and less impressive How much this discrepancy in the findings was due to the actual absence of the organism and how much could be accounted for on the basis of inadequate technique or a not intensive enough search cannot be known In view of the technical difficulties involved, it would seem that positive findings with regard to the incidence of the Pfeiffer bacillus would outweigh, in critical importance, those of a negative character

Jordan (6) summarized the bacteriological findings for the 1918 pandemic very concisely as follows "The upshot of a prodigious amount of work in many countries on the occurrence of the Pfeiffer bacillus in influenza cases seems to be *that this organism is generally, but not invariably, present in the respiratory* tract at some stage of the disease that it is usually—perhaps always—abundant in the human respiratory tract at times when influenza is epidemic, and that in fatal cases it is found frequently in lesions in the lungs and elsewhere" No other bacterium was found with such constancy throughout the pandemic and, though others might sometimes predominate, the Pfeiffer bacillus was almost always there While some investigators were convinced by the 1918 bacteriological studies that Pfeiffer had been confirmed and that *H influenzae* actually was the cause of pandemic influenza, most people, I believe, felt that some other explanation should be sought

A VIRUS IN 1918

Students of influenza who were not convinced of the etiological importance of the Pfeiffer bacillus or any other visible bacterium attempted to demonstrate during the 1918 pandemic that a filtrable virus was causally important The experiments were largely conducted with human volunteers and for the most part were negative Only Selter (30) and Leschke (31), in a very small series of poorly controlled experiments, claim to have produced influenza with bacteriologically sterile filtrates of upper respiratory tract secretions from cases of influenza If the disease supposedly produced in the volunteers was indeed influenza, the findings are probably of little significance because no attempt at segregation or isolation of the individuals was made and the experiments were carried out in September during the initial rapid dissemination of the pandemic Furthermore it is not at all certain from the descriptions given that the illness

supposedly developing as the result of inoculation with the filtered material was indeed influenza

A quite large series of human volunteers were inoculated with filtered influenzal secretions by various investigators under more carefully controlled conditions and among these no cases of influenza developed (13, 14, 32, 33) However, since in these experiments volunteers inoculated with unfiltered secretions also failed to sicken, the filtration experiments are of little or no actual significance

From consideration of the published information on the subject it can be concluded that no certain evidence was adduced during the work of the 1918 pandemic to indicate that a filtrable virus was the causative agent While the view was rather widely held and frequently expressed that a virus probably was the etiological basis for the disease, it actually constituted no more than an ungrounded and gratuitous opinion

The contributions to our knowledge of pandemic influenza gained from study of the 1918 outbreak may be briefly summarized as follows

1 Epidemiological data indicated that the disease was spread by human agency and transmitted from case to case by contact Attempts to prove this method of dissemination in human volunteers, however, failed

2 A mild first wave of influenza in the spring of 1918 preceded the severe second wave of the autumn The first wave resembled clinically and epidemiologically the so-called epidemic or interpandemic influenza which we now know to be caused by a filtrable virus The second wave differed in that it was more severe, more widespread, of greater dispersive power, and, in some places at least, of a different age incidence than the first wave

3 The mild first wave seemed to confer some immunity against the severe second wave, indicating an etiological relationship between the two The immunity was of short duration

4 The morbidity and mortality of pandemic influenza were determined accurately and treated statistically A peculiar age distribution in case incidence and fatalities was shown

5 Extensive bacteriological studies failed to establish Pfeiffer's bacillus as the causative agent or to disprove definitely the etiological claims Differences in the incidence of the organism during the first and second waves were noted

6. No evidence incriminating a filtrable virus as the causative agent was established

From the standpoint of the thesis that I wish to try to develop later on, the significant observations made during the 1918 pandemic are, first, the possible similarities between the first wave and current virus type influenza, second, the immunological relationship between the first and second waves, third, the high incidence of *H influenzae* in the second wave, as contrasted with its low incidence in the first wave; and fourth, certain discrepancies in the assumption that pandemic influenza invariably disseminates by case to case contact

SWINE INFLUENZA

The statement that no animal except man acquires influenza under natural conditions is encountered frequently in the older medical literature From time

to time attention has been called to equine influenza as resembling human influenza in certain of its clinical, pathological, and epidemiological features, but none of the relatively large amount of work done on the disease has indicated more than a superficial similarity, and certainly there has been nothing to indicate a causal relationship between horse and human influenza (34)

It is probable that "new" viruses do not occur these days they are merely new to us as investigators of the diseases in which they are found New infectious diseases, however, do seemingly, even in our times, spring up Such a disease occurred among hogs in the Middle West during the late summer or early autumn of 1918 The exact date and locality of its first appearance remain unknown However, careful observers state that it was prevalent during late August in Illinois By October it was widespread among swine herds in Iowa and other parts of the Middle West

This new disease was not a sporadic and localized outbreak, actually millions of swine became ill and thousands died during the first few months of its prevalence The epizootic persisted in various localities until January of 1919 and reappeared in the autumn and winter of that year almost as extensive and severe as in 1918 It has recurred each year since then but varies annually in its severity and extent

According to Dorset, McBryde, and Niles (35), Dr J S Koen, an Inspector in the Division of Hog Cholera Control of the Bureau of Animal Industry, was the first to recognize the disease as being different from any previously encountered He was so much impressed by the coincidental prevalence of human influenza and by the resemblance of the signs and symptoms seen in man to those occurring at the time in hogs that he became convinced that the two diseases were actually the same He therefore gave the name of "flu" to this new disease of hogs The opinion of Koen that "flu" represented an entirely new swine epizootic disease, and that swine might have been infected in the first instance from man, was shared by some veterinarians and many farmers in the Middle West (36) Furthermore the name "hog flu" or "swine flu" proved a generally accepted designation for the condition, though since it has entered the period of scientific investigation it has been dignified by the name "swine influenza"

In the years immediately following 1918, Koen's contention that a direct causal relationship might exist between the swine and human diseases met considerable verbal resistance Koen however was strong in his convictions, and though frequently called upon to defend them, stuck to them steadfastly A year after his choice of what seemed, at the time, an unpopular name and diagnosis, he defended the choice as follows (37) "I have no apologies to offer for my diagnosis of 'flu' Last fall and winter we were confronted with a new condition, if not a new disease I believe I have as much to support this diagnosis in pigs as the physicians have to support a similar diagnosis in man The similarity of the epidemic among people and the epizootic among pigs was so close, the reports so frequent, that an outbreak in the family would be followed immediately by an outbreak among the hogs, and vice versa, as to present a most striking coincidence if not suggesting a close relation between the two

conditions It looked like 'flu', it presented the identical symptoms of 'flu' and until proved it was not 'flu' I shall stand by that diagnosis "

Allowing for certain differences between hogs and men, swine and pandemic human influenza were indeed very much alike In addition to their coincidental prevalence in the autumn of 1918, the clinical and pathological pictures of the two diseases were similar. In both, fever, anorexia, cough, and other signs referable to the respiratory tract were prominent, a leucopenia occurred in both diseases, and in both the degree of prostration was out of all proportion to the rest of the clinical picture In both diseases the onset was sudden, the course short, and convalescence slow but usually uneventful Both conditions appeared to be highly contagious and to spread over wide geographic areas with the greatest rapidity Death, when it occurred in either the human or swine disease, was frequently the result of a "water-logged", bloody, edematous pneumonia In the swine disease the incidence in any individual herd approached 100 per cent, while the case mortality rate varied between 1 and 4 per cent though it could be considerably higher Pregnant sows frequently aborted or gave birth to premature litters as a result of influenza

It is of course evident that all of these similarities could have been a matter of chance and that one is not warranted in drawing conclusions as to the relationship of the two diseases merely on the basis of clinical and pathological resemblances Their etiological agents should be known and compared In the beginning, or at the time that swine influenza gained prominence as a veterinary problem, a comparison of this nature was impossible because the causative agent of neither disease was known. The etiology of swine influenza was finally determined in 1931 and it proved to be different in character from that of any hitherto known disease of animals or man Because our studies of the etiology of swine influenza were so much like a contracted panorama of the experiences of investigators of the human disease, I am going into some slight detail concerning them

The late Dr Paul Lewis and I began our studies of swine influenza during the autumn of 1928 Two strains of the disease were obtained in Iowa where an epizootic was at the time in progress and no difficulty was encountered in establishing either strain in our laboratory swine at Princeton by intranasal inoculation The respiratory tracts of all experimental animals were examined bacteriologically at autopsy, and much to our pleasant surprise, an organism similar to if not identical with Pfeiffer's *H influenzae* was obtained in pure culture from the first passage swine inoculated with each of the strains (38) The two strains of the disease were maintained by serial nasal passage in swine at 4 or 5 day intervals and the same bacterium was isolated thereafter from all swine infected in later passages, with either strain of the disease, provided they came to autopsy within 7 days following the onset of fever Frequently no organism other than this influenza-like bacillus could be recovered from the lungs or the bronchial exudate of infected animals Here then in swine influenza was an organism like that believed by many to be responsible for influenza in man. The problem of determining the etiology of swine influenza seemed simple

at this stage, for while the bacillus, which we named *Hemophilus influenzae suis*, was not easy to cultivate, it could always be isolated from cases of the experimental disease by appropriate methods In addition, there were numerous cases in which it was the only organism that could be isolated, in these there was no choice but to consider it of etiological importance, unless we wished entirely to deny it a role in the disease

It was of course obvious that the organism should fulfill Koch's postulates if it were actually the cause of swine influenza, and it seemed to do this very thing on our first attempt The pig inoculated intranasally with what we believed to be a pure culture became ill The lesions produced were similar to those of swine influenza, and the organism was recovered in pure culture from the respiratory tract Naturally we were elated, but our joy was short-lived because when we repeated the experiment in a second pig we failed to obtain an infection The animal remained perfectly normal and no lesions suggestive of influenza were to be seen when it was killed after a period of observation Four other pigs inoculated intranasally with pure cultures of the organism likewise remained normal, and we began to doubt that *H influenzae suis* caused swine influenza after all Even now I know of no good explanation for that first positive experiment, because in dozens of attempts since then we have failed completely to cause influenza with pure cultures of the organism

In the autumn of 1929 another epizootic of swine influenza appeared in the Middle West and four fresh strains of infectious material were obtained from Iowa and transmitted to our experimental swine Again *H influenzae suis* was regularly encountered in animals ill of the experimental disease In addition, the organism was cultivated from 6 field cases in 5 different herds Freshly isolated cultures were again found harmless for swine of proved susceptibility

In the autumn of 1930 we obtained two new strains of swine influenza from the annual epizootic in Iowa and established them in our experimental swine at Princeton Again *H influenzae suis* was the predominant or only organism that could be cultivated from the respiratory tracts of the experimental animals, but all efforts to produce the disease with these new cultures were unsuccessful

We were, at this stage of the game, in almost the identical predicament regarding the role of *H influenzae suis* in swine influenza that investigators of human influenza had been at the close of the 1918 pandemic regarding the Pfeiffer bacillus We had an organism which was regularly present in the disease, which was frequently the only organism to be found in relationship to the respiratory tract lesions, but which, administered in pure culture, failed to produce the disease Our transmission experiments had one important advantage over those in which attempts had been made to infect human volunteers with the Pfeiffer bacillus In the human experiments there was no evidence that the volunteers were susceptible to even the crude, supposedly infectious secretions so that it was impossible to know whether the failure of the Pfeiffer bacillus to infect was due to immunity on the part of the volunteers or to the organism's being of no etiological importance In the swine experiments, on the other hand, we could regularly infect with the crude respiratory tract secretions from cases of the

disease so that we knew that failure to induce disease with *H. influenzae suis* was not due to immunity. In fact swine that had failed to become ill as a result of intranasal inoculation with pure cultures of *H influenzae suis* could be readily brought down later by inoculation with crude lung suspensions from infected animals or by exposure to cases of the disease (39) Analogous roles for the Pfeiffer bacillus in human influenza and *H influenzae suis* in swine influenza were strongly suggested by these similarities, and it seemed probable that elucidation of the role played by *H influenzae suis* in the swine disease might shed light on the true relationship of the Pfeiffer bacillus to human pandemic influenza

THE VIRUS OF SWINE INFLUENZA

A few attempts to infect swine by administering bacteriologically sterile Berkefeld filtrates of known infectious material intranasally had been made during the first year's work No illness resembling swine influenza had resulted and the experiments were considered negative By 1930, when *H influenzae suis* had failed so completely to fulfill the requirements of an etiological agent, we were again ready to consider a virus etiology in swine influenza

A total of 10 experiments were conducted inoculating swine with sterile filtrates of known infectious lung and bronchial exudate suspensions Three of these were interpreted as negative, while in the remaining 7 some evidence was obtained that the injected filtrates had contained an infectious agent The illness induced by this filtrable agent, however, was definitely not swine influenza, and for lack of a better name was merely called "filtrate disease" (40)

Clinically the filtrate disease is much milder than swine influenza Sometimes it is so ill defined that infections are difficult to recognize In most cases there is no elevation of temperature while in a few a fever for a day or so is observed This is at marked variance with the 4 to 6 day fevers seen typically in swine influenza The usual signs shown by filtrate-inoculated swine are a moderate and transient apathy, some diminution in appetite for a period not exceeding 3 days, occasionally a slight cough, and, as in swine influenza, a moderate or marked leucopenia The extreme prostration so common in swine influenza is lacking as are also signs indicating extensive lower respiratory tract involvement The lesions at post-mortem are slight as compared with the 4 and 5 lobe pneumonias of swine influenza The lungs show only a scant, scattered, patchy lobular atelectasis involving as a rule not more than small portions of one or two lobes

The experiments indicated the presence, in infectious material from cases of swine influenza, of a filtrable agent possessing slight but definite pathogenic properties for swine when administered intranasally Subsequent study has shown that this agent is a virus *H influenzae suis*, while constantly encountered in animals with typical influenza, was not present in those with filtrate disease, not infrequently their lower respiratory tracts proved bacteriologically sterile

Following the establishment of the presence of a filtrable virus in swine influenza, the situation as to the etiology of the disease itself became even more

confused than it had been when *H influenzae suis* was suspected Here, instead of one agent that could be looked upon as of possible etiological importance, were two such agents The bacterium could not be completely ignored, for, while it was apparently perfectly harmless for swine, its constant presence in so many samples of infectious material from the field and its persistence on serial passage through experimental swine suggested strongly that it must play some role Neither could the filtrable virus be accepted as the cause of the disease because, while it unquestionably possessed pathogenic properties for swine, the mild illness that it caused was certainly not swine influenza Considered in the light of views current that an infectious disease was caused by a single agent, we had reached a point in our experiments where it appeared that we had one too many under suspicion For a while it seemed essential to choose between the two This situation that we found ourselves in was again not peculiar to our own problem with influenza in swine It had its counterpart in human influenza when, during the 1918 pandemic, investigators were trying to decide between Pfeiffer's bacillus and a filtrable virus (hypothetical at the time) as the cause of that disease

It finally developed that we did not have to choose between our two possible causative agents after all, because in the end both proved etiologically essential Swine influenza turned out to be a disease of complex etiology and to be caused by the swine influenza virus and *H influenzae suis* acting together synergistically (40) The virus component, which when given alone caused the mild filtrate disease, differed from any previously known, that is, it seemed to be a "new" virus The bacterial component of the complex, harmless itself but with the virus capable of causing severe and sometimes fatal influenza in swine, was very similar to if not identical with the non indol-producing type of Pfeiffer's *H influenzae*

It was subsequently found that swine recovered from an attack of the mild filtrate disease caused by the virus alone were immune to swine influenza as produced by the combination of virus and bacterium (39) However, as I have intimated earlier, swine that had been inoculated with *H influenzae suis* alone remained fully susceptible to swine influenza (39) It was apparent from this that so far as immunity to the disease was concerned the virus was the important component Furthermore it was found that the virus was strongly pneumotropic and produced infection only when given by way of the respiratory tract Administered by any other route it was completely innocuous However, virus given subcutaneously or intramuscularly, though it failed to induce infection, did produce a solid immunity to swine influenza (39, 11) Advantage has been taken of this observation in the preparation of a vaccine effective against swine influenza

With the clarification of the etiology of swine influenza and the establishment of the fact that both *H influenzae suis* and the virus were causally essential, a further comparison of the swine disease with human influenza was not possible until someone demonstrated whether or not a virus was also involved in the human disease For this there was not long to wait

A FILTRABLE VIRUS IN HUMAN INFLUENZA

In 1933, Smith, Andrewes, and Laidlaw (42) transmitted a disease to ferrets by inoculating intranasally filtrates of pharyngeal washings from cases of epidemic influenza in man The ferret disease proved to be serially transmissible and was characterized by a 2 day incubation period, a diphasic temperature response, symptoms of nasal catarrh, and variable systemic disturbances. The mucous membranes of the nasal passages of ferrets killed during the first or second febrile period were acutely inflamed. Histological examination revealed vascular congestion, dilated lymph channels, numerous leucocytes, and complete disappearance of ciliated cells. The causative agent possessed the properties of a filtrable virus Sera obtained either from recovered ferrets or from patients after an attack of influenza neutralized the virus All the evidence first presented and that obtained later points to the etiological importance of this virus in the disease A laboratory animal for use in studying human influenza was thus finally at hand.

Smith, Andrewes, and Laidlaw also found that swine influenza virus was infectious for ferrets and in them produced an illness similar to that caused by the virus of human origin

The susceptibility of ferrets to swine influenza virus was easily confirmed. However, because difficulty was encountered in administering infectious suspensions intranasally, some of my animals were lightly etherized prior to inoculation (43) Ferrets infected in this way developed a more severe illness than that described by the English investigators, exhibiting an extensive bloody, edematous, lobar pneumonia when autopsied on the 4th or 5th day after infection The pneumonia sometimes terminated fatally. In contrast to influenza in swine, the ferret disease was not modified in character when *H influenzae suis* was administered with the virus

In 1934, Francis (44) recovered a virus from cases of epidemic influenza in Puerto Rico In its earlier passages this virus produced a disease in ferrets similar in all respects to that described for the English virus Francis thus confirmed the observations of Smith, Andrewes, and Laidlaw that a filtrable infectious agent could be transferred from human cases of epidemic influenza to ferrets Since then the observation has been repeatedly confirmed by a great many investigators in all parts of the world Furthermore, Francis found that after several passages in ferrets anesthetized at the time of inoculation, his Puerto Rico virus produced pneumonias similar to those seen in ferrets inoculated in this way with swine virus He pointed out that this suggested adaptation of the human virus to the ferret Similar passage of the English strain also resulted in its acquiring the capacity to produce pulmonary consolidation (45) It was thus apparent, as Francis indicated, that ferret-adapted human influenza virus possessed pathogenic properties for ferrets like those shown from the beginning by swine influenza virus

Andrewes, Laidlaw, and Smith (46) and Francis (44) discovered independently that the human influenza virus could be transmitted to white mice after pre-

liminary passage in ferrets A well-adapted virus regularly killed mice in from 2 to 5 days and at autopsy these animals showed an extensive pneumonia

The virus of swine influenza also proved pathogenic for mice and produced a disease that was indistinguishable clinically or pathologically from that caused by the human agent (46, 47) Like the disease in ferrets, that in mice was not modified when *H influenzae suis* was administered together with the virus

Early serological evidence indicated that all strains of the human influenza virus were identical In 1936, however, Magill and Francis (48) demonstrated, by employing the serum of rabbits early in the immune response to a single injection of a strain of virus, that serological differences between the individual strains of epidemic influenza virus were detectable This observation was substantiated by Smith and Andrewes (49) using convalescent ferret serum Subsequently, serological variations in strains of human influenza virus have been reported by numerous investigators Despite the differences, however, it is clear that the various strains constitute members of the same virus group and are indeed quite closely related Increased immunization of animals, for instance, obliterates the specificity of the immune response, resulting in overlapping of serological or active immunity to the different strains, and the antigen participating in the complement fixation reaction is common to all strains in the group In order to avoid confusion in terminology, influenza viruses classifiable serologically in the same group as the original strain isolated have been designated as influenza A (50) Prior to 1940 no strain of virus other than influenza A was isolated from man

Influenza A virus has been amply shown to be infective for man and capable of reproducing the clinical picture of epidemic influenza when administered by way of the respiratory tract to human volunteers (51, 52, 53)

COMPARISON OF THE VIRUSES OF HUMAN AND SWINE INFLUENZA

The discovery of a virus in human influenza made possible a comparison between it and the virus of swine influenza As I have indicated in the preceding section, the swine influenza virus, like influenza A virus from man, proved pathogenic for both ferrets and mice While there were certain initial differences in pathogenicity, once the human virus was fully adapted it caused a disease in these two species that was indistinguishable clinically or pathologically from that caused by swine influenza virus

But the similarity between the swine and human influenza viruses did not end with their like pathogenicity for ferrets and mice It was found that they immunized against one another (45, 47) Thus ferrets or mice recovered from infection with swine influenza virus were not only immune to reinfection with that agent but also usually resisted infection with the human influenza virus In like manner, animals first infected with human virus were found to be immune later to the swine virus Such cross immunity suggested a close immunological relationship between the viruses from man and swine That the two agents were not actually identical, however, could be shown serologically each virus was completely neutralized by its homologous immune serum while the heterolo-

gous immune serum usually failed to neutralize (54, 55, 47) Because of the minor serological diversity mentioned earlier as existing among the human viruses, certain strains appeared immunologically more closely related to the swine virus than did certain others To the best of my knowledge, however, no authentic human influenza virus strain immunologically identical with swine influenza virus has ever been recovered from man The conclusion reached from consideration of cross-immunity and cross-neutralization experiments was that the viruses of human and swine influenza were rather closely related but not identical.

The swine influenza virus particle was found by ultrafiltration studies to be the same size as the human influenza virus particle (56)

With the discovery that a filtrable virus was involved in human influenza and that this agent bore such a striking similarity to the virus component of the swine influenza etiological complex, another point in common between the influenzas of swine and man seemed to have been established. The unfortunate part, so far as complete comparison was concerned, was that the human virus under study had not come from pandemic influenza but from the milder interpandemic disease.

THE SUSCEPTIBILITY OF SWINE TO HUMAN INFLUENZA VIRUS

In view of the reputed background of swine influenza and its history of having appeared as a new disease in 1918 at the time of the great pandemic, it seemed of interest to study the behavior of the human influenza A virus in swine This was done by Elkeles (57) and by Francis and me (58), and our results were in essential agreement It was found that swine, inoculated intranasally with human influenza virus alone, developed an extremely mild illness similar clinically and at autopsy to the filtrate disease caused by infection with swine influenza virus alone When small amounts of a culture of *H influenzae suis* were administered with the virus a somewhat more severe febrile illness usually resulted This was similar to swine influenza though clinically milder The animals were seldom ill and febrile for longer than 2 or 3 days, and the extreme prostration so frequent in swine influenza was not observed At autopsy the pneumonia encountered was of the same character as that seen in swine influenza but much less extensive The disease caused in swine by the human virus and *H influenzae suis* can best be characterized as a mild swine influenza similar qualitatively but differing quantitatively from the typical disease occurring naturally in this species

Of further interest to the present discussion was the observation that not all pigs inoculated with the human virus and the swine bacterium developed a more severe illness than that caused by the virus alone Some exhibited symptoms and pulmonary lesions like those seen in the filtrate disease, and in these it could be shown that *H influenzae suis* had failed to become established with the virus Instances of this nature have never been encountered in swine inoculated with swine influenza virus and *H influenzae suis* The facts would lead one to conclude that, in swine, the human virus possesses less invasive power than does

the swine virus Furthermore, the human virus seems to be inherently less capable of acting synergistically with a second organism than is swine influenza virus In addition, while one of the characteristic features of swine influenza is its extreme contagiousness, the disease caused in swine by infection with human influenza virus and *H influenzae suis* is of only low communicability

Thus, in swine, human influenza A virus differs from swine influenza virus in three rather outstanding features first, it is less capable of acting synergistically with a second organism, second, it causes a clinically milder disease, and third, it is less highly contagious If differences of this character prevailed between two agents causing disease in man it would be anticipated that outbreaks caused by each agent would be at wide variance with one another, both clinically and epidemiologically

So far as our information at this stage of the story went, the human virus was specific for man though it could infect swine under experimental conditions In like manner, the swine virus was specific for swine though there was the historical evidence that it might have derived originally from man Our views as to this species specificity of the two viruses had to be modified shortly however

ANTIBODIES TO SWINE INFLUENZA VIRUS IN HUMAN SERA

With the discovery of the human influenza virus and its striking similarity in many respects to the swine virus, new interest was aroused in the possibility that the swine virus might have at one time been a human pathogen The most satisfactory way of obtaining information as to the past prevalence of a virus in a population is by studying the virus-neutralizing antibody content of sera from individuals in that population

As I have already indicated, sera from animals recovered from infection with human influenza virus neutralized that agent but usually not the swine virus Conversely, the sera of animals recovered from infection with swine virus neutralized that agent but usually not the human virus Thus we had some assurance that the antibody findings fairly accurately reflected the past history of animals so far as their previous experiences with either swine or human influenza virus were concerned It seemed reasonable therefore that some information of a similar nature for man might be derived from like studies of the antibody content of human sera

The results obtained both in England (54) and in this country (59, 60) were quite unexpected in that it was found that the sera of almost all adults studied neutralized swine influenza virus whereas the sera of only 3 of 41 children under 10 years of age exercised a similar effect The sera of some of the children and between one half and two thirds of the adults neutralized influenza A virus, as might have been expected from our knowledge of the recent past prevalence of human influenza

So far as our serological findings went, then, they indicated that almost all adults had undergone a past infection with a virus of the swine influenza type, all but 3 of 41 children under 10 in the series had evidently not undergone this infection Interpreted in the usual way for viruses in general, these data indi-

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cated the past widespread prevalence in human beings of a virus of the swine influenza type 10 or more years prior to that in which the neutralization tests were carried out (1935) The reputed history that swine influenza appeared first in 1918 serves to date the time of prevalence of the agent responsible for the swine influenza virus antibodies in human sera Since swine influenza virus is not currently present in man and, to judge from the results of the studies of the antibody content of human sera, ceased infecting man extensively sometime prior to 1925, it seems quite apparent that its period of prevalence in man was in all probability in the neighborhood of 1918 and shortly thereafter Laidlaw (61) and I (62) have expressed the opinion therefore that the presence of swine influenza virus-neutralizing antibodies in human adult sera can best be explained on the basis of previous infection of those individuals with a virus bearing the antigenic composition of the one which now causes influenza in swine This virus, according to our viewpoint, is the one that was widely prevalent in man in 1918 and probably for several succeeding years and which was involved in the great pandemic We have therefore interpreted the presence of swine virus antibodies in human sera as indicative of a previous infection with virus of the 1918 pandemic type

This theory or interpretation has from time to time been attacked by quite a number of good people doing influenza research, most notably Burnet, Francis, and Andrewes, and cannot be said to be generally accepted Most of the objectors have explained the presence of swine virus antibodies in human sera as resulting from repeated exposure to human influenza virus It is known from work with experimental animals that, though one exposure to human type virus results in the formation of neutralizing antibody to only that virus, multiple exposures may eventually result in the appearance of antibodies that neutralize both the human virus and the swine virus On this basis the presence of swine virus-neutralizing antibody in the sera of adults is explained as resulting from many previous infections with human virus, conversely, absence of swine virus antibody in the sera of younger people is accounted for as due to insufficient opportunities for infection with human virus to broaden the antibody spectrum to include swine virus This line of reasoning seems awkward to me, and it also seems particularly fortuitous, too much so, that this general influenza antibody, so-called, should happen to react selectively with a virus of the antigenic composition of swine influenza virus While I do not want to take up a lot of time on the matter, I should just like to point out before I leave the subject that quite a high proportion of human adult sera (35 of 112 in my own series (60)) neutralized only the swine virus and were without significant effect on the human agent In these, then, the added assumption would have to be made that the "specific" human virus antibody disappeared while the "non-specific" swine virus antibody persisted a highly artificial rigmarole to have to go through to avoid a simple and direct explanation I still think that the presence of swine influenza virus-neutralizing antibody in human serum may be an indication of a previous infection with virus of that antigenic type, and that in all probability the swine virus was at one time, probably during the 1918 pandemic, a human pathogen

THE NATURAL OCCURRENCE OF HUMAN INFLUENZA VIRUS INFECTION IN SWINE

Proof that the present human influenza virus can invade swine under natural conditions does not have to be so circuitously arrived at In the spring of 1937 a serum sample from a pig, sent to the laboratory from the New Jersey State Prison Farm at Bordentown, was tested for human and swine influenza virus-neutralizing antibodies Surprisingly the sample neutralized the human but not the swine virus This was the first field sample of pig serum, from a number that had been tested, that we had found to contain antibodies effective against the human agent The unexpected finding led us to study the swine drove at the Prison Farm more completely Twenty-eight other pigs were bled and their sera tested for swine and human influenza virus antibodies All 28 sera neutralized the human virus (63) None neutralized the swine virus During December of 1936 and January of 1937, there had been a number of cases clinically diagnosed as influenza both among the inmates at the prison furnishing garbage for the piggery and among the attendants at the farm At another state institution, the New Jersey State Home for Boys at Jamesburg, there had been an outbreak of influenza among the inmates during the same winter This had been studied by Stokes and his coworkers (64) and definitely established as influenza by the isolation of typical influenza A virus The swine drove at this institution was cared for by the inmates and seemed to offer further favorable material for study Sera were obtained from 20 of the pigs that had lived through the winter during which influenza had prevailed in the human population Fifteen of the sera neutralized human influenza virus but not the swine virus and the remaining 5 sera neutralized neither

It is believed on the basis of the known behavior of swine to experimental infection that the antibodies resulted from actual infection of the animals with human influenza virus and that, in both herds studied, a widespread infection of human origin had occurred Neither swine outbreak was recognized at the time of its occurrence but this is not surprising because, even under conditions of experimental infection of swine with human influenza virus alone, the resulting disease is so mild and ill-defined as to be difficult of certain recognition How the virus was transferred to swine is unknown, though presumably it was either by direct exposure to human cases or through the medium of garbage contaminated by virus

The observations just outlined, by demonstrating that human influenza virus of the type prevalent during the winter of 1936–37 was transmitted to swine under natural conditions, furnish evidence that a similar transmission from man to swine might readily have occurred in 1918 If it transferred in 1936–37 as our experimental evidence indicates that it did, I see no justification in the various objections that have been raised to the acceptance of the evidence that the pandemic virus similarly transferred, probably with its Pfeiffer bacillus co-conspirator, in 1918 and has continued since then as what we know today as swine influenza virus The failure of recent strains of human influenza virus to cause widely disseminated porcine epizootics like those caused annually in the Middle West by swine influenza virus may be explained by the low contagiousness, when in swine, of the current human influenza viruses

From the evidence presented it seems to me that the conclusion is justifiable that neither the current human influenza virus nor the swine influenza virus is strictly specific for the species in which it now occurs, the human virus can transfer under natural conditions to swine, and a large body of indirect evidence indicates that the swine virus actually was, within our own time, a human pathogen.

THE RELATIONSHIP BETWEEN PANDEMIC AND INTERPANDEMIC INFLUENZA

The question of the relationship between pandemic influenza and that which occurs between pandemics has engaged a great deal of attention and speculation in the past A number of observers (6) of the 1918 influenza have pointed out that the first wave of that outbreak was not unlike influenza of the interpandemic years and would probably have attracted very little attention had it not been followed by the severe second wave.

A view that has been widely expressed by those who believed the 1918 pandemic to be of virus etiology is that two immunologically different viruses are involved in pandemic and interpandemic influenza Prior to 1940 we had definite knowledge of only one human influenza virus, namely, A While different strains of this A virus showed minor antigenic differences these were not marked enough to interfere seriously with a uniform immunological response to the agent In 1940, however, an influenza virus immunologically entirely distinct from A was discovered by Francis who designated the new agent influenza virus B (65) We now have good evidence of an indirect character that the B type virus formed the etiological basis for an extensive epidemic of influenza originally recognized in California during the early months of 1936 The agent, so far as we know, did not reappear as the cause of any widespread outbreak again until in the first two months of 1940 when it formed the basis for an extensive outbreak in the southeastern part of the country Both of these epidemics with which we now know influenza virus B to have been associated were of the same general character as those caused every other year, since its discovery, by the influenza A virus The point that I should like to make in connection with the B type virus is that it was what might be termed a "new" virus, so far as could be told by the general low level of antibodies against it in human sera, and appeared upon the scene without causing any catastrophic outbreak such as the 1918 pandemic had been. It therefore does not necessarily follow that the appearance of an influenza virus, apparently new to a fully susceptible population, is going to result in an outbreak of pandemic proportions

This question of the relationship of interpandemic influenza to the pandemic disease is one of very great importance to us right now We know that the relatively mild influenza that appears every other winter, or more frequently, has a virus as its cause We know a great deal about this virus and much more is being learned daily because it is being intensively studied in a number of different laboratories What we do not know is whether all of the information that we are accumulating about interpandemic influenza and its causative viruses will be of any use to us in understanding or combating the next pandemic

No one can have more than an opinion concerning the relationship of a disease of unknown etiology occurring 25 years ago and one, whose cause we know, occurring today I should like briefly to outline my own opinion concerning the relationship of pandemic influenza to the current interpandemic disease and, in so doing, to detail my own views as to the probable etiological character of the pandemic disease

I shall start with the assumption, to which I think everyone will now agree, that current epidemic influenza has a virus cause As I indicated earlier, we have evidence that influenza A virus has caused outbreaks at least every other year since its discovery during the winter of 1932–33 Influenza B virus caused outbreaks in the early months of 1936 and 1940 Serological studies of human material would seem to indicate that, of the two agents, the A virus is the more common and in the past has been the more prevalent Certainly we have information concerning the occurrence of virus A in human outbreaks chronologically farther into the past There is no reason to suppose that the 1932–33 outbreak in which the influenza A virus was first identified was the original outbreak with which it was associated It seems more likely that it had been causing influenza for many years before the scientific finger was finally placed upon it and that this influenza had been the usual characteristically mild interpandemic type In the spring of 1918 there occurred an outbreak of mild influenza that was geographically of wider distribution than usual, but certainly of no wider distribution than was the epidemic of 1936–37, for instance, known to be of virus cause This mild 1918 outbreak, as investigators who saw it commented, would probably have attracted no more attention than any other interpandemic occurrence of the disease had it not been followed in the autumn by a severe second wave, the 1918 pandemic There would seem to be no logical basis for deciding on clinical grounds that the mild first wave of 1918 was significantly different from the occurrences of interpandemic influenza that preceded it and that have recurred since the pandemic of 1918 ran its course Because we have no basis for comparison other than the supposed clinical similarities between the 1918 first wave and interpandemic influenza, it would seem that we were justified in drawing no other conclusion from the information available than that the two were probably causally related This being the case, then the best opinion would seem to be that the mild first wave of 1918 influenza was an outbreak of virus influenza To make the immunological surmising, in which I shall later have to indulge, effective, it will be necessary to assume that the influenza virus involved was of the A type This is not an unreasonable assumption because the A virus, from all the available information, is and has been the more common type prevailing in interpandemic influenza

There are two features of the first wave other than its clinical mildness, to which I should like to call especial attention as being of particular significance to the present discussion First, to judge from the reports of bacteriological studies, the outbreak was not notably associated with a coincident widespread Pfeiffer bacillus infection In this respect, the mild first wave differed markedly from the pandemic wave in which the incidence of infection with the influenza

bacillus was extremely high. Second, most of the evidence available indicates that the first wave conferred a perfectly definite and clear-cut immunity to the pandemic wave This is extremely important so far as orienting the agent responsible for the pandemic is concerned If individuals recovered from infection with the virus that we have hypothecated as the cause of the first wave were indeed immune to the agent responsible for the pandemic wave, the only admissible conclusion that can be drawn is that a virus, antigenically identical with or closely related to that of the first wave, was also primarily associated with the pandemic wave We thus reach the point where out deducible evidence indicates involvement of the influenza virus in both waves How then can we account for the striking differences in the epidemiology and clinical severity that existed between the two waves? True we do have evidence that the Pfeiffer bacillus was widespread among cases of the pandemic wave and practically lacking among those of the first wave, but if the two viruses were similar, and our immunological evidence suggests this, it is unreasonable to suppose that in one wave the Pfeiffer bacillus would play a role and not play a similar role in the other wave.

We have assumed for the sake of the present discussion that the current influenza A virus, or one of its very closely related ancestors, was the agent responsible for the first wave We thus know quite a lot about this first wave virus We know among other things that, in addition to man, it was pathogenic for ferrets, mice, and swine It seems, in retrospect, a shame that someone did not think to put pharyngeal washings from cases of the pandemic disease into the noses of ferrets, mice, or swine, so that we might also have the pandemic virus for comparison Of the dozens of people studying influenza at the time, no one seems to have done this, at least no investigator did it purposely But this oversight may not have been too serious, because Nature seems to have tried its own hand in the investigation As I have mentioned earlier, at about the time the pandemic was getting under way in the Middle West a new disease appeared among the hogs out there This ailment bore such a striking clinical and pathological resemblance to influenza and coincided so frequently in its onset with the occurrence of pandemic influenza among the human inhabitants of the farm that a causal relationship between the two diseases seemed certain to observers on the spot This 1918 influenza of swine very obligingly became firmly established in its new host and has persisted up to the present day so that there has been ample opportunity to study the infectious agents it seems to have preserved for us from its 1918 human prototype Now to me it appears immaterial, so far as the eventual end result is concerned, whether some investigator during the 1918 pandemic discovered the cause of pandemic influenza by inoculating material from patients into swine, or whether the pigs just picked up the infection on their own and preserved its etiological character for discovery later on By both methods the same objective is achieved In fact, when the matter is considered more circumspectly there are certain apparent advantages in letting the pig and Nature work the thing out themselves By this I mean that a more accurate conception of the true etiological picture has in all likeli-

hood been obtained than if experiments with ferrets, mice, and swine had been conducted in 1918 Had ferrets or mice been used at that time the virus would no doubt have been discovered but, since the Pfeiffer bacillus plays no role in the infection in these two species, the significance of the concomitant presence of this bacterium in the infectious process would probably have been missed The significance of the complex infection might even have been missed had the experiments been conducted initially in swine, because the tendency among virus-minded investigators then, as now, has been to filter away and discard any bacterium found in association with a filtrable agent The way the thing worked out under natural conditions in the farm yards of the Middle West was probably, after all, the best because, not only was the virus preserved for later study, but the bacterial component of the etiological complex was segregated from among the large mixture of other bacteria with which it was confusedly mixed in man It thus seems entirely likely that in swine influenza we have a replica of the etiology of the human pandemic disease of 1918 Also, in swine it appears that we have a species of animal reflecting, more nearly than any other, the various reactions of man to influenzal infection

Assuming all this to be reasonably true we have, from the work I have described earlier in these lectures, a tangible explanation for the differences between pandemic and interpandemic influenza I shall try to rationalize the differences observed on the basis of the known differences in behavior of human and swine influenza virus in swine Human influenza A virus, as I have told you, produces a mild illness in swine, and this illness is only moderately and irregularly accentuated when *H influenzae suis* is administered with the virus The disease is not more than moderately contagious Swine influenza virus alone also produces only a mild illness, but this illness is very markedly accentuated when *H influenzae suis* is given with the virus The disease is very highly contagious An attack of human influenza A virus usually renders an animal immune to swine influenza virus Influenza A virus in swine is thus an agent of relatively low communicability and with little capacity to act synergistically with a second organism, while swine influenza virus is one of extremely high communicability and with a marked capacity to act synergistically with *H influenzae suis* Though these viruses are immunologically related and possess very similar pathogenic properties for ferrets and mice, their widely differing behavior in swine demonstrates their potentialities to induce diseases of widely differing epidemiological, clinical, and pathological patterns Translated into the terms of the first and second waves of influenza in 1918, we find the influenza A virus, or one of its ancestors, during the first wave causing a mild disease of low dispersiveness in which neither the Pfeiffer bacillus nor any other bacterium regularly played a significant role During the second wave we find a virus of the swine influenza type causing a severe disease of high dispersiveness in which the Pfeiffer bacillus and numerous other bacteria played a constant and lethal role

The human influenza A virus in its role as a human or swine pathogen behaves like a complete infectious unit and has little capacity to accentuate its patho-

genicity by synergistic activity with a bacterium The pandemic virus, on the other hand, in its role as a human or swine pathogen behaves like an incomplete infectious unit in that it possesses a marked capacity to accentuate its pathogenicity by synergistic activity with a bacterium It seems to have an inherent avidity for combining with a second organism. In all likelihood, at the outset, it begins its course alone and causes a clinical picture much like that caused by the interpandemic virus. However, once it is in contact with a bacterium for which it has an avidity, it immediately sets up the alliance which converts it to a complete infectious unit, and from there progresses on its true pandemic course In the case of the swine influenza virus in swine, the avidity of the virus is definitely and rather specifically limited to *H influenzae suis* Whether the pandemic virus has a specific avidity for *H influenzae* is still, for want of definite experimental evidence, a matter of opinion My own opinion, based on three considerations, is that the pandemic virus does have a specific avidity for the Pfeiffer bacillus and that the infectious unit for pandemic influenza is "virus plus *Hemophilus*" just as in swine influenza the infectious unit is a similar complex This does not mean that other bacteria do not play a possibly significant role in the pathogenesis of the disease In swine influenza one not infrequently sees cases badly infected by secondary invaders, but these complicating bacteria are secondary, not to the virus, but to the complex of "virus plus *Hemophilus*" In such cases the *Hemophilus* can usually be demonstrated, although it may be far from the predominating organism

The three considerations upon which I base my opinion that the pandemic virus has a specific avidity for the Pfeiffer bacillus, and with it constitutes the infectious unit, are as follows —

First, the view is in accord with the recorded bacteriological findings of the 1918 pandemic and satisfactorily answers the objections raised to the acceptance of the Pfeiffer bacillus as the sole etiological agent The organism was found frequently enough in cases to indicate its probably almost universal presence and was certainly much more constantly present than any other organism at the site of the specific lesions in the respiratory tract The view cannot be challenged on the basis of the organism's widespread prevalence in normals, its serological diversity, its failure to infect human beings when given in pure culture, or its failure to be the predominant bacterium in the respiratory tract flora of many cases Second, our own experiences in incriminating *H. influenzae suis* in the etiology of swine influenza bear such a striking parallel to the recorded efforts to elucidate the relationship of *H influenzae* to pandemic influenza that I cannot but feel that the similarities are more than coincidental Third, if, as seems likely, the pandemic virus transferred from man to swine in 1918 and if, as also seems likely, the Pfeiffer bacillus transferred with it, it would be rather illogical to suppose that two agents bearing such an intimate relationship to each other in inducing swine influenza should not have borne a similar relationship to each other in their preceding host Certainly of all the horde of bacteria occurring in pandemic influenza it would be most peculiar to have a non-essential

one choose to accompany the virus in transferring to a new host For these reasons I believe that the infectious unit in pandemic influenza is composed of a specific complex of virus plus Pfeiffer's bacillus

On this basis, then, the two waves of influenza in 1918 were etiologically quite distinct The first was caused by a virus of the current human type capable of acting alone as a complete infectious unit The second wave was caused by an immunologically related but not identical virus which required the synergistic activity of the Pfeiffer bacillus to convert it into a complete infectious unit The former virus has persisted and causes periodic outbreaks of what we term now epidemic influenza The latter virus has apparently disappeared as a human pathogen but persists in swine A generic relationship between the two viruses in 1918 would be difficult to establish My own opinion is that the two waves may have occurred independently of one another and their apparent chronological relationship may have been purely a matter of coincidence I believe that the pandemic outbreak might have come whether the mild spring wave had occurred or not An attractive subject for speculation, however, is the possibility that the virus of the second wave arose as a mutation or adaptation from the virus of the first wave The antigenic relationship between the two viruses is not out of line with the possibility, and certainly some explanation such as this would render much easier a visualization of the origin of the strain responsible for the pandemic The mutation would have been one which altered the parent virus in such a fashion that it required the synergistic activity of a specific bacterium to complete it as an infective unit If such a mutation occurred it apparently altered the antigenic composition of the virus also, because the present swine virus and the present influenza A viruses are antigenically quite different even though they do cross-immunize against one another in experimental animals Whether the next pandemic will be caused by a virus antigenically like influenza A, influenza B, or swine influenza cannot be predicted, but whatever its antigenic composition, I am most certain that it will of itself be an incomplete infectious unit and will require the good offices of the Pfeiffer bacillus in carrying out its depredations

This brings us back to the point of answering the question as to whether the information that we are accumulating about interpandemic influenza and its causative viruses will be of any use to us in understanding and combating the next pandemic I think that it will, because what evidence we have indicates that, even in a complex infection, such as swine influenza is and pandemic influenza is indicated to be, the virus component of the complex is the immunologically important portion In swine influenza, for instance, if one immunizes an animal to the virus, it is immune to the total complex of virus and bacterium For this reason it seems to me that everything we discover about the recognition, handling, and control of the current viruses will be applicable to the next pandemic virus whatever its antigenic character may be The trick will be to recognize it and isolate it in time to use it One suggestion that might be made is that, on the chance that pandemic history may repeat itself and give us a virus

of the swine antigenic type to deal with, we should include this virus in our human vaccines, or at least have it in readiness for inclusion if the next pandemic should happen to be of the swine type

EPIDEMIOLOGY OF SWINE INFLUENZA

One of the largest puzzles so far as the epidemiology of influenza is concerned has to do with the whereabouts of the causative virus between outbreaks We know that influenza A virus recurs in epidemic form at roughly two year intervals The two known visitations of influenza B virus were spaced by a four year interval, and outbreaks of pandemic influenza occur at intervals of over a decade Where are the causative viruses during the intervals that they are not producing influenza in man? I have indicated the possibility that the 1918 pandemic virus may have arisen as a mutant of the current epidemic influenza A virus, but this suggestion, even if correct, gets us little further along the way towards an understanding, because it does not explain the inter-epidemic whereabouts of the virus in which the mutation may have occurred

Swine influenza until recently posed the same epidemiological question concerning the inter-epizootic whereabouts of its virus In a disease as highly contagious as swine influenza one does not worry too much about its mode of dissemination once an epizootic has started However, getting that first case, which presumably will seed the outbreak, is the puzzle Also, getting the disease from one drove to another in extremely rapid succession offers certain other difficulties of explanation Swine influenza epizootics have occurred in the Middle West each year since 1918 Characteristically they begin explosively late in October or early in November (35, 36) The build-up of cases is extremely rapid and one gains the impression that the disease has arisen at many different foci simultaneously By this I mean that when the hogs on one farm sicken, those on other farms in the region are very likely to come down at about the same time The pattern of apparent dissemination is very reminiscent of that seen among army camps and civilian communities at the outset of the 1918 human pandemic The disease, if it is actually disseminated, gets spread about in miraculously and unbelievably rapid fashion After the initial widespread outbreak, fresh swine droves become infected in smaller and smaller numbers until by late December, as a rule, the epizootic appears to have run its course and swine influenza disappears as a farm infection until the following October or November

The rapidity of spread of pandemic influenza in 1918 was explained, at least partially, on the basis of the availability of modern means of transportation in scattering the infectious agent, through the medium of infected passengers, over geographically large areas Veterinarians, influenced probably by views of this character, have similarly rationalized the apparent rapid dissemination of swine influenza While hogs as a rule do not travel except to market, and this is a one-way trip, their owners do visit around and in some obscure way are supposed to spread disease from farm to farm Actually it is probable that the problems of the epidemiology of modern swine influenza are very similar to those of human

pandemic influenza occurring before the era of rapid travel I went into some detail earlier in outlining 18th century views concerning the epidemiology of their influenza, and I should like to have you recall those and bear them in mind now, while I am outlining a partial elucidation of some of the problems of the epidemiology of swine influenza

THE ROLE OF THE SWINE LUNGWORM IN THE EPIDEMIOLOGY OF SWINE INFLUENZA

Because the swine lungworm has been found to enter prominently into the epidemiology of swine influenza, I had best briefly outline its life cycle as determined by the Hobmaiers (66) and by Schwartz and Alicata (67) The swine lungworm (I have worked largely with a mixture of *Metastrongylus elongatus* and *Choerostrongylus pudendotectus*) is a nematode parasitic in the bronchioles of the bases of the lungs of swine The adult female lungworm lays fully embryonated eggs in the bronchi of the swine she infests These eggs are coughed up and swallowed, and reach the outer world in the feces Their further development then is dependent upon their being ingested by earthworms Once within the earthworm, the lungworm eggs hatch and the larvae develop to the third or infective larval stage, usually localizing in the calciferous glands and hearts of the parasitized earthworm They persist in this stage until the earthworm host is eaten by a pig In the pig the lungworms undergo two further developmental stages, finally reaching the swine respiratory tract by way of the blood stream and lymphatics, where they become adults The whole of this cycle can occupy a span of several years for its completion, or under the most favorable conditions can be completed in a little more than a month

About three years ago it was discovered that the lungworm could serve as intermediate host for the swine influenza virus (68) It was found that the larvae developing from lungworm ova laid during the time the host pig is undergoing an attack of swine influenza, or even from those laid for at least a short period after recovery, are carriers of swine influenza virus A most puzzling feature of the transmission of swine influenza virus by the lungworm, however, is that virus cannot be detected by direct means either in the larvae in their earthworm intermediate hosts or in the adult lungworm after transmission to its definitive host, the pig It appears to be present in an occult or masked form, evidence of its presence in its intermediate host is furnished only by its subsequent behavior under very specialized conditions in the swine respiratory tract Swine infested with lungworms that are carrying this masked virus do not as a rule come down directly with swine influenza, as might be expected Instead they remain to all outward appearances perfectly normal pigs However, though they probably do not realize it, they are in a very precarious situation so far as their eventual well being is concerned, because all that is required to bring them down with a severe or even fatal influenzal infection is the application of some stimulus, of itself relatively harmless Several such provocative stimuli have been used, but the one that has proved most regularly effective consists in the administration of multiple intramuscular injections of the bac-

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terium *H influenzae suis* These injections are ordinarily begun some weeks after the lungworm infestation has become established in the experimental swine, and are spaced at intervals of eight days Influenza usually follows the second or third injection

While only little is known concerning the mechanism involved in the transmission of swine influenza virus by lungworms, some facts indicating its probable applicability in the epidemiology of the disease are at hand It has been found, for instance, that swine influenza virus can persist without giving any detectable evidence of its presence for at least as long as 32 months in third stage lungworm larvae in their earthworm intermediate hosts, and for at least an additional three months in association with adult lungworms in the swine respiratory tract (69) This constitutes a total elapsed time—between the case of swine influenza originally supplying the virus and the hog eventually becoming infected with it—of almost three years, and is roughly three times the amount which must be accounted for to explain the survival of the virus from one epizootic to the next

Another fact concerning the phenomenon seems to have a suggestive bearing upon the seasonal epidemicity of swine influenza Transmission of swine influenza virus by way of lungworms takes place as outlined if the experiments are conducted between October and April, that is, during the fall, winter, and spring months (69) However, experiments carried out from May to October have as yet, with only one exception, during three summers yielded negative results The failure of the virus to cause infection by way of its intermediate host during the summer fits well with the known seasonal incidence of swine influenza under field conditions

In order to establish decisively that the lungworm was actually the reservoir and intermediate host of the virus in natural outbreaks of swine influenza, field studies were necessary These were of two types In the first, an attempt was made to learn whether or not lungworm larvae naturally infected with masked swine influenza virus could be demonstrated in earthworms gathered on Midwestern farms where swine influenza was of annual occurrence In the second, we tried to provoke influenza in field swine which it was believed might be carrying the virus These animals were obtained during an inter-epizootic period from a farm whose swine drove gave a history of annual outbreaks of influenza. Both sets of experiments resulted positively (70).

In the first set, swine to which lungworm-infested earthworms from Midwestern farms were fed came down with characteristic swine influenza when an appropriate provocative stress was applied This indicated that the lungworm under natural field conditions may be a carrier of masked swine influenza virus and a potential source of infection to any swine infested by it

The second set of field experiments, with Middle Western swine obtained from their home farm during an inter-epizootic period, were particularly enlightening concerning one phase of the epidemiology of swine influenza Of three swine brought to the laboratory from Iowa late in September, swine influenza virus infections were provoked in two by appropriate procedures in November

These three animals had been picked at random from a drove of about 50 on the Iowa farm An assumption which seems warranted, in view of the fact that masked swine influenza virus had been demonstrated in lungworm larvae in earthworms from the same farm, is that these swine were carriers of masked swine influenza virus when they were received at the laboratory and that this masked virus was in association with lungworms acquired back on the home farm The swine influenza virus responsible for the disease developing in these swine is considered to be the same that they would have sickened of had they been left on the Iowa farm with their 50 whole and half brothers and sisters Since there is no reason for suspecting that the three swine chosen represented an unusual sample of the drove, the finding that at least two were carriers of masked virus suggested an extremely high carrier rate for the drove as a whole

The finding of this high carrier rate suggests that the apparent paradox of swine influenza spreading throughout a drove and from farm to farm—faster than we realize it can, on the basis of any known incubation period—may not be paradoxical at all Instead of the virus going like wildfire from drove to drove and throughout a drove, the field experiments indicate that it is probably widely seeded before the outbreak and merely provoked almost simultaneously The great rapidity of spread therefore is more apparent than real and represents a delusion resulting from the provocation of widely disseminated masked virus by a stimulus common to large geographical areas This stimulus is probably meteorological in character Under experimental conditions in the laboratory, however, though season determines whether or not infections can be elicited in prepared swine, the exact type of "weather," which seemingly serves to provoke swine influenza infections in the field, has not been successfully imitated

The concept of the epidemiology of swine influenza just outlined is, according to current epidemiologic views, unorthodox in at least three respects In the first place, a highly contagious disease like swine influenza is not usually thought of as requiring the services of an intermediate host Ordinarily such a host is sought for or considered requisite only in those diseases that do not transmit naturally by contact In the case of swine influenza, however, one large period of the epidemiologic cycle, the inter-epizootic phase, becomes readily understandable only if the services of an intermediate host capable of maintaining the virus from one epizootic to the next can be invoked Once an epizootic has got under way, of course, it is possible for the disease to be disseminated by contact Robert Johnson, of the 18th century, was quoted earlier to the effect that in the case of human influenza he did not wish to be understood to mean that that disease was not at all contagious but rather that it appeared to be possible for cases to arise without previous direct contact The facts in the case of swine influenza are reminiscent of those older contentions regarding human

A second unorthodox feature of the epidemiology of swine influenza, ered as a contagious disease, is the lack of chronological relationship be seeding of the causative virus and the onset of the two events are considered to coincide quite closely under way when the causative agent becomes

to be no more lag between seeding and onset than can be accounted for by the so-called incubation period In the case of swine influenza, however, seeding of masked virus in the swine respiratory tract by way of the lungworm can take place months before the infection finally becomes manifest In the field it seems likely that the masked virus is widely seeded throughout a swine population long before evidence of its presence becomes apparent late in October or November

A third unorthodox feature of the epidemiology of swine influenza, considered as a contagious disease, concerns the lack of direct continuity between cases Ordinarily a contagious disease spreads from sick to well and, if complete knowledge were available, it is believed that each new case could be traced to some preceding one In swine influenza, however, the epizootic starts so explosively and the disease is disseminated so rapidly, even throughout an individual swine drove, that continuity of infection from one case to the next cannot be established in the majority of instances Here the virus responsible for each of the primary infections stems from a case that occurred at least nine months previously, and during the interim has resided in an intermediate host, in a masked, non-infective form From such initial or first cases the virus can, and undoubtedly does on occasion, spread by ordinary contact from sick to normal swine

The mechanism by which swine influenza virus survives from one outbreak to the next and finally becomes established afresh each year as a disease-producing agent in swine is far from simple Even with an understanding of the role played by the lungworm as reservoir and intermediate host for the virus, the epidemiology of swine influenza rivals in complexity the conceptions held by Johnson and his contemporaries concerning 18th century influenza of man In fact, so close is the parallel between the epidemiologic facts of present-day swine influenza and the epidemiologic phantasies of 18th century human influenza that the question is raised whether we are warranted in assuming the half-amused manner in which we have viewed the multiplicity of "causes" predicated in 18th century epidemiology In swine influenza, for instance, weather and season play the decisive role in determining whether or not masked virus, within its lungworm intermediate host, can be provoked to infectivity This is clearly identifiable with the "remote cause" of earlier days The provocative stress necessary to render masked swine influenza virus infective is simply the older "exciting cause," a little more explicitly defined The "predisposing cause" of older days is of little importance in the epidemiology of swine influenza, so far as we know at present, because those swine not immune by virtue of a previous attack regularly sicken whenever exposed to infective swine influenza virus and *H influenzae suis* Immunity would of course constitute an absence of predisposition in the older sense The "proximate cause," that which was directly responsible for the signs and symptoms of illness, we identify in the case of swine influenza as the swine influenza virus acting in concert with *H influenzae suis* It is evident, I believe, that, though visualization of the manner in which swine influenza virus can spread from one animal to another once the first cases are established is relatively easy, an explanation of the initiation of those first cases

requires a coincidental complexity of factors that are but little more simple than those accepted by Johnson back in the 18th century in explaining the origin of his first cases of human influenza

Some of you may have inferred from my comparison of the epidemiologies of current swine influenza and 18th century human influenza that I was implying the presence of an intermediate host for the causative agent of the human disease similar to the lungworm for swine influenza Such an implication is not intended, and the only reason for making the comparison is to indicate the many similarities in the problems involved prior to the apparent solution, or at least better understanding, of the natural history of the swine disease Information concerning the epidemiology of swine influenza is of value to students of the human disease mainly insofar as it suggests analogies There are indeed many analogies, as I have tried to point out, but unfortunately for a better understanding of the epidemiology of the human disease, a helminthic parasite of man that might substitute for the lungworm of swine as an intermediate and reservoir host for influenza virus is not apparent Similarities in the epidemiologic patterns of the two diseases are, however, so close as to suggest that pre-epidemic seeding of the causative agent of the human disease must take place as it does in the swine disease, even though a helminth host like the lungworm cannot be implicated as the disseminating agent in man It seems to me that the almost unbelievable rapidity of spread of human pandemic influenza, as well as a number of its other puzzling epidemiologic features, can be more simply and effectively explained on the assumption that the causative agent is pre-seeded widely and subsequently almost simultaneously provoked, than it can be by trying to base the entire explanation on the thesis of case to case transfer

During the course of the lectures that I am about to conclude I have tried to outline the old, intermediate, and contemporary contributions to our knowledge of pandemic influenza The old had to do with various epidemiologic aspects that I felt were applicable even today and that certainly have their counterparts in certain phases of the epidemiology of swine influenza upon which I have drawn heavily in indicating possible analogies The intermediate contributions introduced the Pfeiffer bacillus into the picture and rather insecurely oriented it there They also lent accuracy to our epidemiological information Contemporary contributions largely concerned the introduction of a virus into our concept It is evident from the manner in which contributions to our knowledge concerning pandemic influenza can be classified chronologically that thought on the subject, like the pandemics themselves, has been cyclic During the 1918 pandemic most of the huge volume of work concerned the role played by the influenza bacillus in the disease This was because at the close of the 1889 pandemic Pfeiffer had focused the attention of the scientific world upon this particular organism as the cause of influenza, and most people had considered the claims for it legitimate enough to warrant further study It was investigated to the almost complete exclusion of other possibilities in 1918

Now the almost complete focus of scientific attention is upon the influenza viruses and little interest is expressed any more in the Pfeiffer bacillus I

be willing to wager that if we were to have another great pandemic, say in 1945, those reviewing the scientific work of the period afterward would find that study of the viruses had been as preponderant and exclusive in 1945 as had been study of the Pfeiffer bacillus in 1918

To me, this extreme centralization of scientific effort upon what may be just one phase of the problem seems rather foolish and short-sighted The next epidemic, like those of the past, will undoubtedly be explosively sudden in its onset and will pass in a relatively short period of time At the most, we shall have probably not more than three months for our observations and investigations, and I fervently hope that some of us, at least, can keep off the virus band wagon long enough to find out two bits of other information In addition to studying the virus of the next pandemic, it seems to me that we should determine once and for all what, if any, role the Pfeiffer bacillus plays in the etiology of the pandemic disease We should also consider the epidemiologic pattern critically enough to learn whether or not person to person contact adequately explains the dissemination of the disease, or whether, as in swine influenza, prepandemic seeding of the causative agent plays a role Only by completely understanding a disease can we ever hope to control it

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